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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/19, C07K 14/535, A61K 38/19, C12N 5/06, A61K 48/00

A1

(11) International Publication Number: WO 97/12977

(43) International Publication Date: 10 April 1997 (10.04.97)

(21) International Application Number: PCT/US96/15935

(22) International Filing Date: 4 October 1996 (04.10.96)

(30) Priority Data:
60/004,382 5 October 1995 (05.10.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 60/004,382 (CON)
Filed on 5 October 1995 (05.10.95)

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL G-CSF RECEPTOR AGONISTS

(57) Abstract

Disclosed are G-CSF receptor agonists proteins, DNAs which encode the G-CSF hematopoietic receptor agonists proteins, methods of making the G-CSF hematopoietic receptor agonists proteins and methods of using the G-CSF hematopoietic receptor agonists proteins.

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NOVEL G-CSF RECEPTOR AGONISTS

The present application claims priority under 35 USC §119(e) of United States provisional application Serial No. 60/004,382 filed October 05, 1995.

Field of the Invention

The present invention relates to human G-CSF receptor agonists with activity on hematopoietic cell differentiation and expansion.

Background of the Invention

The human blood-forming (hematopoietic) system replaces a variety of white blood cells (including neutrophils, macrophages, and basophils/mast cells), red blood cells (erythrocytes) and clot-forming cells (megakaryocytes/platelets). The hematopoietic systems of the average male has been estimated to produce on the order of 4.5×10^{11} granulocytes and erythrocytes every year, which is equivalent to an annual replacement of total body weight (Dexter et al., *BioEssays*, **2**;154-158, 1985).

It is believed that small amounts of certain hematopoietic growth factors account for the differentiation of a small number of progenitor "stem cells" into the variety of blood cell lines, for the tremendous proliferation of those lines, and for the ultimate differentiation of mature blood cells from those lines. Because the hematopoietic growth factors are present in extremely small amounts, the detection and identification of these factors has relied upon an array of assays which as yet only distinguish among the different factors on the basis of stimulative effects on cultured cells under artificial conditions.

U.S. Patent 4,999,291 discloses DNA and methods for making G-CSF the disclosure of which is incorporated herein by reference in it entirety.

U.S. Patent 4,810,643 relates to DNA and methods of making G-CSF and Cys to Ser substitution variants of G-CSF.

Kuga et al. (*Biochem. + Biophys. Res. Comm.* **159**:103-111, 1988) made a series of G-CSF variants to partially define the structure-function relationship. Kuga et al. found that internal and C-terminal deletions abolished activity, while N-terminal deletions of up to 11 amino acids and amino acid substitutions at positions 1, 2 and 3 were active.

Watanabe et al. (*Anal. Biochem.* **195**:38-44, 1991) made a variant to study G-CSF receptor binding in which amino acids 1 and 3 were changed to Tyr for radioiodination of the protein. Watanabe et al. found this Tyr^1, Tyr^3 G-CSF variant to be active.

WO 95/27732 describes, but does not show that the molecule has biological activity, a circularly permuted G-CSF ligand with a breakpoint at positions 68/69 creating a circularly permuted G-CSF ligand with a new N-terminus at the original position 69 of G-CSF and a new C-terminus at the original position 68 of G-CSF. WO 95/27732 also discloses circularly permuted GM-CSF, IL-2 and IL-4.

Rearrangement of Protein Sequences

In evolution, rearrangements of DNA sequences serve an important role in generating a diversity of protein structure and function. Gene duplication and exon shuffling provide an important mechanism to rapidly generate diversity

and thereby provide organisms with a competitive advantage, especially since the basal mutation rate is low (Doolittle, *Protein Science* **1**:191-200, 1992).

The development of recombinant DNA methods has made it possible to study the effects of sequence transposition on protein folding, structure and function. The approach used in creating new sequences resembles that of naturally occurring pairs of proteins that are related by linear reorganization of their amino acid sequences (Cunningham, et al., *Proc. Natl. Acad. Sci. U.S.A.* **76**:3218-3222, 1979; Teather & Erfle, *J. Bacteriol.* **172**: 3837-3841, 1990; Schimming et al., *Eur. J. Biochem.* **204**: 13-19, 1992; Yamiuchi and Minamikawa, *FEBS Lett.* **260**:127-130, 1991: MacGregor et al., *FEBS Lett.* **378**:263-266, 1996). The first in vitro application of this type of rearrangement to proteins was described by Goldenberg and Creighton (*J. Mol. Biol.* **165**:407-413, 1983). A new N-terminus is selected at an internal site (breakpoint) of the original sequence, the new sequence having the same order of amino acids as the original from the breakpoint until it reaches an amino acid that is at or near the original C-terminus. At this point the new sequence is joined, either directly or through an additional portion of sequence (linker), to an amino acid that is at or near the original N-terminus, and the new sequence continues with the same sequence as the original until it reaches a point that is at or near the amino acid that was N-terminal to the breakpoint site of the original sequence, this residue forming the new C-terminus of the chain.

This approach has been applied to proteins which range in size from 58 to 462 amino acids (Goldenberg & Creighton, *J. Mol. Biol.* **165**:407-413, 1983; Li & Coffino, *Mol. Cell. Biol.* **13**:2377-2383, 1993). The proteins examined have represented a broad range of structural classes, including proteins that contain predominantly α-helix (interleukin-4;

Kreitman et al., *Cytokine* **7**:311-318, 1995), βsheet (interleukin-1; Horlick et al., *Protein Eng.* **5**:427-431, 1992), or mixtures of the two (yeast phosphoribosyl anthranilate isomerase; Luger et al., *Science* **243**:206-210, 1989). Broad categories of protein function are represented in these sequence reorganization studies:

Enzymes

T4 lysozyme	Zhang et al., *Biochemistry* **32**:12311-12318 (1993); Zhang et al., *Nature Struct. Biol.* **1**:434-438 (1995)
dihydrofolate reductase	Buchwalder et al., *Biochemistry* **31**:1621-1630 (1994); Protasova et al., *Prot. Eng.* **7**:1373-1377 (1995)
ribonuclease T1	Mullins et al., *J. Am. Chem. Soc.* **116**:5529-5533 (1994); Garrett et al., *Protein Science* **5**:204-211 (1996)
Bacillus β-glucanse	Hahn et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:10417-10421 (1994)
aspartate transcarbamoylase	Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984 (1993)
phosphoribosyl anthranilate isomerase	Luger et al., *Science* **243**:206-210 (1989); Luger et al., *Prot. Eng.* **3**:249-258 (1990)
pepsin/pepsinogen	Lin et al., *Protein Science* **4**:159-166 (1995)

glyceraldehyde-3-phosphate dehydrogenase	Vignais et al., *Protein Science* **4**:994-1000 (1995)
ornithine decarboxylase	Li & Coffino, *Mol. Cell. Biol.* **13**:2377-2383 (1993)
yeast phosphoglycerate dehydrogenase	Ritco-Vonsovici et al., *Biochemistry* **34**:16543-16551 (1995)
Enzyme Inhibitor	
basic pancreatic trypsin inhibitor	Goldenberg & Creighton, *J. Mol. Biol.* **165**:407-413 (1983)
Cytokines	
interleukin-1β	Horlick et al., *Protein Eng.* **5**:427-431 (1992)
interleukin-4	Kreitman et al., *Cytokine* **7**:311-318 (1995)
Tyrosine Kinase Recognition Domain	
α-spectrin SH3 domain	Viguera, et al., *J. Mol. Biol.* **247**:670-681 (1995)
Transmembrane Protein	
omp A	Koebnik & Krämer, *J. Mol. Biol.* **250**:617-626 (1995)

Chimeric Protein

interleukin-4–*Pseudomonas* exotoxin fusion molecule	Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893 (1994).

The results of these studies have been highly variable. In many cases substantially lower activity, solubility or thermodynamic stability were observed (*E. coli* dihydrofolate reductase, aspartate transcarbamoylase, phosphoribosyl anthranilate isomerase, glyceraldehyde-3-phosphate dehydrogenase, ornithine decarboxylase, omp A, yeast phosphoglycerate dehydrogenase). In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart (basic pancreatic trypsin inhibitor, T4 lysozyme, ribonuclease T1, Bacillus β-glucanase, interleukin-1β, αspectrin SH3 domain, pepsinogen, interleukin-4). In exceptional cases, an unexpected improvement over some properties of the natural sequence was observed, e.g., the solubility and refolding rate for rearranged α-spectrin SH3 domain sequences, and the receptor affinity and anti-tumor activity of transposed interleukin-4–*Pseudomonas* exotoxin fusion molecule (Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893, 1994; Kreitman et al., *Cancer Res.* **55**:3357-3363, 1995).

The primary motivation for these types of studies has been to study the role of short-range and long-range interactions in protein folding and stability. Sequence rearrangements of this type convert a subset of interactions that are long-range in the original sequence into short-range interactions in the new sequence, and vice versa. The fact that many of these sequence rearrangements are able to attain a conformation with at least some activity is persuasive evidence that protein folding occurs by multiple

folding pathways (Viguera, et al., *J. Mol. Biol.* **247**:670-681, 1995). In the case of the SH3 domain of αspectrin, choosing new termini at locations that corresponded to β -hairpin turns resulted in proteins with slightly less stability, but which were nevertheless able to fold.

The positions of the internal breakpoints used in the studies cited here are found exclusively on the surface of proteins, and are distributed throughout the linear sequence without any obvious bias towards the ends or the middle (the variation in the relative distance from the original N-terminus to the breakpoint is ca. 10 to 80% of the total sequence length). The linkers connecting the original N- and C-termini in these studies have ranged from 0 to 9 residues. In one case (Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984, 1993), a portion of sequence has been deleted from the original C-terminal segment, and the connection made from the truncated C-terminus to the original N-terminus. Flexible hydrophilic residues such as Gly and Ser are frequently used in the linkers. Viguera, et al.(*J. Mol. Biol.* **247**:670-681, 1995) compared joining the original N- and C- termini with 3- or 4-residue linkers; the 3-residue linker was less thermodynamically stable. Protasova et al. (*Protein Eng.* **7**:1373-1377, 1994) used 3- or 5-residue linkers in connecting the original N-termini of *E. coli* dihydrofolate reductase; only the 3-residue linker produced protein in good yield.

Summary of the Invention

The modified human G-CSF receptor agonists of the present invention can be represented by the Formula:

$$X^1\text{-}(L)_a\text{-}X^2$$

wherein;

a is 0 or 1;

X^1 is a peptide comprising an amino acid sequence corresponding to the sequence of residues n+1 through J;

X^2 is a peptide comprising an amino acid sequence corresponding to the sequence of residues 1 through n;

n is an integer ranging from 1 to J-1; and

L is a linker.

In the formula above the constituent amino acids residues of human G-CSF are numbered sequentially 1 through J from the amino to the carboxyl terminus. A pair of adjacent amino acids within this protein may be numbered n and n+1 respectively where n is an integer ranging from 1 to J-1. The residue n+1 becomes the new N-terminus of the new G-CSF receptor agonist and the residue n becomes the new C-terminus of the new G-CSF receptor agonist.

The present invention relates to novel G-CSF receptor agonists of the following formula:

```
1                                   10
Xaa Xaa Xaa Gly Pro Ala Ser Ser Leu Pro Gln Ser Xaa

                    20
Leu Leu Xaa Xaa Xaa Glu Gln Val Xaa Lys Xaa Gln Gly Xaa Gly

    30                                  40
```

Ala Xaa Leu Gln Glu Xaa Leu Xaa Ala Thr Tyr Lys Leu Xaa Xaa

Xaa Glu Xaa Xaa Val Xaa Xaa Gly His Ser Xaa Gly Ile Pro Trp

Ala Pro Leu Ser Ser Xaa Pro Ser Xaa Ala Leu Xaa Leu Ala Gly

Xaa Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu

Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu

Xaa Thr Leu Gln Xaa Asp Val Ala Asp Phe Ala Xaa Thr Ile Trp

Gln Gln Met Glu Xaa Xaa Gly Met Ala Pro Ala Leu Gln Pro Thr

Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Xaa Gln Xaa Xaa Ala

Gly Gly Val Leu Val Ala Ser Xaa Leu Gln Xaa Phe Leu Xaa Xaa

Ser Tyr Arg Val Leu Xaa Xaa Leu Ala Gln Pro (SEQ ID NO:1)

wherein

Xaa at position 1 is Thr, Ser, Arg, Tyr or Gly;
Xaa at position 2 is Pro or Leu;
Xaa at position 3 is Leu, Arg, Tyr or Ser;
Xaa at position 13 is Phe, Ser, His, Thr or Pro;
Xaa at position 16 is Lys, Pro, Ser, Thr or His;
Xaa at position 17 is Cys, Ser, Gly, Ala, Ile, Tyr or Arg;
Xaa at position 18 is Leu, Thr, Pro, His, Ile or Cys;
Xaa at position 22 is Arg, Tyr, Ser, Thr or Ala;
Xaa at position 24 is Ile, Pro, Tyr or Leu;
Xaa at position 27 is Asp, or Gly;
Xaa at position 30 is Ala, Ile, Leu or Gly;
Xaa at position 34 is Lys or Ser;
Xaa at position 36 is Cys or Ser;
Xaa at position 42 is Cys or Ser;
Xaa at position 43 is His, Thr, Gly, Val, Lys, Trp, Ala, Arg, Cys, or Leu;
Xaa at position 44 is Pro, Gly, Arg, Asp, Val, Ala, His, Trp, Gln, or Thr;
Xaa at position 46 is Glu, Arg, Phe, Arg, Ile or Ala;
Xaa at position 47 is Leu or Thr;
Xaa at position 49 is Leu, Phe, Arg or Ser;

Xaa at position 50 is Leu, Ile, His, Pro or Tyr;
Xaa at position 54 is Leu or His;
Xaa at position 64 is Cys or Ser;
Xaa at position 67 is Gln, Lys, Leu or Cys;
Xaa at position 70 is Gln, Pro, Leu, Arg or Ser;
Xaa at position 74 is Cys or Ser;
Xaa at position 104 is Asp, Gly or Val;
Xaa at position 108 is Leu, Ala, Val, Arg, Trp, Gln or Gly;
Xaa at position 115 is Thr, His, Leu or Ala;
Xaa at position 120 is Gln, Gly, Arg, Lys or His
Xaa at position 123 is Glu, Arg, Phe or Thr
Xaa at position 144 is Phe, His, Arg, Pro, Leu, Gln or Glu;
Xaa at position 146 is Arg or Gln;
Xaa at position 147 is Arg or Gln;
Xaa at position 156 is His, Gly or Ser;
Xaa at position 159 is Ser, Arg, Thr, Tyr, Val or Gly;
Xaa at position 162 is Glu, Leu, Gly or Trp;
Xaa at position 163 is Val, Gly, Arg or Ala;
Xaa at position 169 is Arg, Ser, Leu, Arg or Cys;
Xaa at position 170 is His, Arg or Ser;

wherein optionally 1-11 amino acids from the N-terminus and 1-5 from the C-terminus can be deleted; and

wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini at amino acids;

38-39	62-63	123-124
39-40	63-64	124-125
40-41	64-65	125-126
41-42	65-66	126-127
42-43	66-67	128-129
43-44	67-68	128-129
45-46	68-69	129-130
48-49	69-70	130-131
49-50	70-71	131-132
52-53	71-72	132-133
53-54	91-92	133-134
54-55	92-93	134-135
55-56	93-94	135-136
56-57	94-95	136-137
57-58	95-96	137-138
58-59	96-97	138-139
59-60	97-98	139-140
60-61	98-99	140-141
61-62	99-100	141-142
		or 142-143.

The G-CSF receptor agonists of the present invention may contain amino acid substitutions, deletions and/or insertions and may also have amino acid deletions at either/or both the N- and C- termini.

The more preferred breakpoints at which new C-terminus and N-terminus can be made are; 38-39, 39-40, 40-41, 41-42, 48-49, 53-54, 54-55, 55-56, 56-57, 57-58, 58-59, 59-60, 60-61, 61-62, 62-63, 64-65, 65-66, 66-67, 67-68, 68-69, 69-70, 96-97, 125-126, 126-127, 127-128, 128-129, 129-130, 130-131, 131-132, 132-133, 133-134, 134-135, 135-136, 136-137, 137-138, 138-139, 139-140, 140-141 and 141-142.

The most preferred breakpoints at which new C-terminus and N-terminus can be made are; 38-39, 48-49, 96-97, 125-126, 132-133 and 141-142.

A preferred embodiment of the present invention the linker (L) joining the N-terminus to the C-terminus is a polypeptide selected from the group consisting of:

GlyGlyGlySer (SEQ ID NO:2);
GlyGlyGlySerGlyGlyGlySer (SEQ ID NO:61);
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer (SEQ ID NO:62);
SerGlyGlySerGlyGlySer (SEQ ID NO:63);
GluPheGlyAsnMet (SEQ ID NO:64);
GluPheGlyGlyAsnMet (SEQ ID NO:65);
GluPheGlyGlyAsnGlyGlyAsnMet (SEQ ID NO:66); and
GlyGlySerAspMetAlaGly (SEQ ID NO:67).

The present invention also encompasses recombinant human G-CSF receptor agonists co-administered or sequentially with one or more additional colony stimulating factors (CSF) including, cytokines, lymphokines, interleukins, hematopoietic growth factors which include but

are not limited to GM-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "colony stimulating factors" or "CSF"). These co-administered mixtures may be characterized by having the usual activity of both of the peptides or the mixture may be further characterized by having a biological or physiological activity greater than simply the additive function of the presence of the G-CSF receptor agonists or the second colony stimulating factor alone. The co-administration may also provide an enhanced effect on the activity or an activity different from that expected by the presence of the G-CSF ligand or the second colony stimulating factor. The co-administration may also have an improved activity profile which may include reduction of undesirable biological activities associated with native human G-CSF. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 can be co-administered with the polypeptides of the present invention.

In addition, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before the expanded cells are infused into patients

Brief Description of the Figures

Figure 1 schematically illustrates the sequence rearrangement of a protein. The N-terminus (N) and the C-terminus (C) of the native protein are joined through a linker, or joined directly. The protein is opened at a breakpoint creating a new N-terminus (new N) and a new C-terminus (new-C) resulting in a protein with a new linear amino acid sequence. A rearranged molecule may be synthesized *de novo* as linear molecule and not go through the steps of joining the original N-terminus and the C-terminus and opening of the protein at the breakpoint.

Figure 2 shows a schematic of Method I, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the amino acid 11 (a.a. 1- 10 are deleted) through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 3 shows a schematic of Method II, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined without a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the original N-terminus and a new C-terminus created at amino acid 96 of the original sequence.

Figure 4 shows a schematic of Method III, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to amino acid 1 through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Detailed Description of the Invention

Receptor agonists of the present invention may be useful in the treatment of diseases characterized by decreased levels of granulocytes of the hematopoietic system.

A G-CSF receptor agonist may be useful in the treatment or prevention of neutropenia. Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. G-CSF receptor agonists may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. The present peptide may be useful in treating such hematopoietic deficiency.

Another aspect of the present invention provides plasmid DNA vectors for use in the method of expression of these novel G-CSF receptor agonists. These vectors contain the novel DNA sequences described above which code for the novel polypeptides of the invention. Appropriate vectors which can transform host cells capable of expressing the G-CSF receptor agonists include expression vectors comprising nucleotide sequences coding for the G-CSF receptor agonists joined to transcriptional and translational regulatory

sequences which are selected according to the host cells used. Vectors incorporating modified sequences as described above are included in the present invention and are useful in the production of the modified G-CSF receptor agonist polypeptides. The vector employed in the method also contains selected regulatory sequences in operative association with the DNA coding sequences of the invention and capable of directing the replication and expression thereof in selected host cells.

As another aspect of the present invention, there is provided a novel method for producing the novel family of human G-CSF receptor agonists. The method of the present invention involves culturing suitable cells or cell line, which has been transformed with a vector containing a DNA sequence coding for expression of the novel G-CSF receptor agonist polypeptide. Suitable cells or cell lines may include various strains of bacteria such as *E. coli*, yeast, mammalian cells, or insect cells may be utilized as host cells in the method of the present invention.

Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a therapeutically effective amount of one or more of the G-CSF receptor agonists of the present invention in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

The dosage regimen involved in a metnod for treating the above-described conditions will be determined by the attending physician considering various factors which modify the action of drugs, e.g. the condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, a daily regimen may be in the range of 0.5 - 150 μg/kg of non-glycosylated G-CSF receptor agonists protein per kilogram of body weight. Dosages would be adjusted relative to the activity of a given receptor agonist and it would not be unreasonable to note that dosage regimens may include doses as low as 0.1 microgram and as high as 1 milligram per kilogram of body weight per day. In addition, there may exist specific circumstances where dosages of G-CSF receptor agonist would be adjusted higher or lower than the range of 0.5 - 150 micrograms per kilogram of body weight. These include co-administration with other CSF or growth factors; co-administration with chemotherapeutic drugs and/or radiation; the use of glycosylated G-CSF receptor agonists; and various patient-related issues mentioned earlier in this section. As indicated above, the therapeutic method and compositions may also include co-administration with other human factors. A non-exclusive list of other appropriate hematopoietins, CSFs and interleukins for simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "colony stimulating factors"), or combinations thereof. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638

can be co-administered with the polypeptides of the present invention.

The G-CSF receptor agonists of the present invention may be useful in the mobilization of hematopoietic progenitors and stem cells in peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation. Hematopoietic growth factors, including G-CSF and GM-CSF, have been shown to enhance the number of circulating progenitors and stem cells in the peripheral blood. This has simplified the procedure for peripheral stem cell collection and dramatically decreased the cost of the procedure by decreasing the number of pheresis required. The G-CSF receptor agonist of the present invention may be useful in mobilization of stem cells and further enhance the efficacy of peripheral stem cell transplantation.

The G-CSF receptor agonists of the present invention may also be useful in the ex vivo expansion of hematopoietic progenitors. Colony stimulating factors (CSFs), such as G-CSF, have been administered alone, co-administered with other CSFs, or in combination with bone marrow transplants subsequent to high dose chemotherapy to treat the neutropenia and which is often the result of such treatment. However the period of severe neutropenia may not be totally eliminated. The myeloid lineage, which is comprised of monocytes (macrophages), granulocytes (including neutrophils) and megakaryocytes, is critical in preventing infections and bleeding which can be life-threatening. Neutropenia may also be the result of disease, genetic disorders, drugs, toxins, radiation and many therapeutic treatments such as conventional oncology therapy.

Bone marrow transplants have been used to treat this patient population. However, several problems are associated

with the use of bone marrow to reconstitute a compromised hematopoietic system including: 1) the number of stem cells in bone marrow or other tissues, such as spleen or peripheral blood, is limited, 2) Graft Versus Host Disease, 3) graft rejection and 4) possible contamination with tumor cells. Stem cells and progenitor cells make up a very small percentage of the nucleated cells in the bone marrow, spleen and peripheral blood. It is clear that a dose response exists such that a greater number of multipotential hematopoietic progenitors will enhance hematopoietic recovery. Therefore, the in vitro expansion of stem cells should enhance hematopoietic recovery and patient survival. Bone marrow from an allogeneic donor has been used to provide bone marrow for transplant. However, Graft Versus Host Disease and graft rejection limit bone marrow transplantation even in recipients with HLA-matched sibling donors. An alternative to allogeneic bone marrow transplants is autologous bone marrow transplants. In autologous bone marrow transplants, some of the patient's own marrow is harvested prior to myeloablative therapy, e.g. high dose chemotherapy, and is transplanted back into the patient afterwards. Autologous transplants eliminate the risk of Graft Versus Host Disease and graft rejection. However, autologous bone marrow transplants still present problems in terms of the limited number of stems cells in the marrow and possible contamination with tumor cells. The limited number of multipotential hematopoietic progenitors may be overcome by ex-vivo expansion of the multipotential hematopoietic progenitors. In addition, stem cells can be specifically isolated based on the presence of specific surface antigens such as CD34+ in order to decrease tumor cell contamination of the marrow graft.

The following patents contain further details on separating stem cells, CD34+ cells, culturing the cells with

hematopoietic factors, the use of the cells for the treatment of patients with hematopoietic disorders and the use of hematopoietic factors for cell expansion and gene therapy.

5,061,620 relates to compositions comprising human hematopoietic stem cells provided by separating the stem cells from dedicated cells.

5,199,942 describes a method for autologous hematopoietic cell transplantation comprising: (1) obtaining hematopoietic progenitor cells from a patient; (2) ex-vivo expansion of cells with a growth factor selected from the group consisting of IL-3, flt3 ligand, c-kit ligand, GM CSF, IL-1, GM-CSF/IL-3 fusion protein and combinations thereof; (3) administering cellular preparation to a patient.

5,240,856 relates to a cell separator that includes an apparatus for automatically controlling the cell separation process.

WO 91/16116 describes devices and methods for selectively isolating and separating target cells from a mixture of cells.

WO 91/18972 describes methods for in vitro culturing of bone marrow, by incubating suspension of bone marrow cells, using a hollow fiber bioreactor.

WO 92/18615 relates to a process for maintaining and expanding bone marrow cells, in a culture medium containing specific mixtures of cytokines, for use in transplants.

WO 93/08268 describes a method for selectively expanding stem cells, comprising the steps of (a) separating CD34+

stem cells from other cells and (b) incubating the separated cells in a selective medium, such that the stem cells are selectively expanded.

WO 93/18136 describes a process for in vitro support of mammalian cells derived from peripheral blood.

WO 93/18648 relates to a composition comprising human neutrophil precursor cells with a high content of myeloblasts and promyelocytes for treating genetic or acquired neutropenia.

WO 94/08039 describes a method of enrichment for human hematopoietic stem cells by selection for cells which express c-kit protein.

WO 94/11493 describes a stem cell population that are CD34+ and small in size, which are isolated using a counterflow elutriation method.

WO 94/27698 relates to a method combining immunoaffinity separation and continuous flow centrifugal separation for the selective separation of a nucleated heterogeneous cell population from a heterogeneous cell mixture.

WO 94/25848 describes a cell separation apparatus for collection and manipulation of target cells.

The long term culturing of highly enriched CD34+ precursors of hematopoietic progenitor cells from human bone marrow in cultures containing IL-1α, IL-3, IL-6 or GM-CSF is discussed in Brandt et al (*J. Clin. Invest.* **86**:932-941, 1990).

One aspect of the present invention provides a method for selective ex-vivo expansion of stem cells. The term "stem cell" refers to the multipotential hematopoietic cells as well as early myeloid progenitor and precursors cells which can be isolated from bone marrow, spleen or peripheral blood. The term "expansion" refers to the proliferation and differentiation of the cells. The present invention provides a method for selective ex-vivo expansion of stem cells, comprising the steps of; (a) separating stem cells from other cells, (b) culturing the separated stem cells with a selective medium which contains a G-CSF receptor agonist and optionally a second colony stimulating factor, and (c) harvesting the cultured stems cells. Stem cells, as well as committed progenitor cells destined to become neutrophils, erythrocytes, platelets, etc., may be distinguished from most other cells by the presence or absence of particular progenitor marker antigens, such as CD34, that are present on the surface of these cells and/or by morphological characteristics. The phenotype for a highly enriched human stem cell fraction is reported as CD34+, Thy-1+ and lin-, but it is to be understood that the present invention is not limited to the expansion of this stem cell population. The CD34+ enriched human stem cell fraction can be separated by a number of reported methods, including affinity columns or beads, magnetic beads or flow cytometry using antibodies directed to surface antigens such as the CD34+. Further, physical separation methods such as counterflow elutriation may be used to enrich hematopoietic progenitors. The CD34+ progenitors are heterogeneous, and may be divided into several sub-populations characterized by the presence or absence of co-expression of different lineage associated cell surface associated molecules. The most immature progenitor cells do not express any known lineage associated markers, such as HLA-DR or CD38, but they may express CD90(thy-1). Other surface antigens such as CD33, CD38,

CD41, CD71, HLA-DR or c-kit can also be used to selectively isolate hematopoietic progenitors. The separated cells can be incubated in selected medium in a culture flask, sterile bag or in hollow fibers. Various colony stimulating factors may be utilized in order to selectively expand cells. Representative factors that have been utilized for ex-vivo expansion of bone marrow include, c-kit ligand, IL-3, G-CSF, GM-CSF, IL-1, IL-6, IL-11, flt-3 ligand or combinations thereof. The proliferation of the stem cells can be monitored by enumerating the number of stem cells and other cells, by standard techniques (e.g. hemacytometer, CFU, LTCIC) or by flow cytometry prior and subsequent to incubation.

Several methods for ex-vivo expansion of stem cells have been reported utilizing a number of selection methods and expansion using various colony stimulating factors including c-kit ligand (Brandt et al., *Blood* **83**:1507-1514, 1994; McKenna et al., *Blood* **86**:3413-3420, 1995), IL-3 (Brandt et al., *Blood* **83**:1507-1514, 1994; Sato et al., *Blood* **82**:3600-3609, 1993), G-CSF (Sato et al., *Blood* **82**:3600-3609, 1993), GM-CSF (Sato et al., *Blood* **82**:3600-3609, 1993), IL-1 (Muench et al., *Blood* **81**:3463-3473, 1993), IL-6 (Sato et al., *Blood* **82**:3600-3609, 1993), IL-11 (Lemoli et al., *Exp. Hem.* **21**:1668-1672, 1993; Sato et al., *Blood* **82**:3600-3609, 1993), flt-3 ligand (McKenna et al., *Blood* **86**:3413 3420, 1995) and/or combinations thereof (Brandt et al., *Blood* **83**:1507 1514, 1994; Haylock et al., *Blood* **80**:1405-1412, 1992, Koller et al., *Biotechnology* **11**:358-363, 1993; Lemoli et al., *Exp. Hem.* **21**:1668-1672, 1993), McKenna et al., *Blood* **86**:3413-3420, 1995; Muench et al., *Blood* **81**:3463-3473, 1993; Patchen et al., *Biotherapy* **7**:13-26, 1994; Sato et al., *Blood* **82**:3600-3609, 1993; Smith et al., *Exp. Hem.* **21**:870-877, 1993; Steen et al., *Stem Cells* **12**:214-224, 1994; Tsujino et al., *Exp. Hem.* **21**:1379-1386, 1993). Among the individual

colony stimulating factors, hIL-3 has been shown to be one of the most potent in expanding peripheral blood CD34+ cells (Sato et al., *Blood* **82**:3600-3609, 1993; Kobayashi et al., *Blood* **73**:1836-1841, 1989). However, no single factor has been shown to be as effective as the combination of multiple factors. The present invention provides methods for ex vivo expansion that utilize novel G-CSF receptor agonists.

Another aspect of the invention provides methods of sustaining and/or expanding hematopoietic precursor cells which includes inoculating the cells into a culture vessel which contains a culture medium that has been conditioned by exposure to a stromal cell line such as HS-5 (WO 96/02662, Roecklein and Torok-Strob, *Blood* **85**:997-1105, 1995) that has been supplemented with a G-CSF receptor agonist of the present invention.

Another projected clinical use of growth factors has been in the in vitro activation of hematopoietic progenitors and stem cells for gene therapy. Due to the long life-span of hematopoietic progenitor cells and the distribution of their daughter cells throughout the entire body, hematopoietic progenitor cells are good candidates for ex vivo gene transfection. In order to have the gene of interest incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication. Hematopoietic stem cells cycle at a very low frequency which means that growth factors may be useful to promote gene transduction and thereby enhance the clinical prospects for gene therapy. Potential applications of gene therapy (review Crystal, *Science* **270**:404-410, 1995) include; 1) the treatment of many congenital metabolic disorders and immunodeficiencies (Kay and Woo, *Trends Genet.* **10**:253-257, 1994), 2) neurological disorders (Friedmann, *Trends Genet.* **10**:210-214, 1994), 3) cancer (Culver and

Blaese, *Trends Genet.* **10**:174-178, 1994) and 4) infectious diseases (Gilboa and Smith, *Trends Genet.* **10**:139-144, 1994).

There are a variety of methods, known to those with skill in the art, for introducing genetic material into a host cell. A number of vectors, both viral and non-viral have been developed for transferring therapeutic genes into primary cells. Viral based vectors include; 1) replication deficient recombinant retrovirus (Boris-Lawrie and Temin, *Curr. Opin. Genet. Dev.* **3**:102-109, 1993; Boris-Lawrie and Temin, *Annal. New York Acad. Sci.* **716**:59-71, 1994; Miller, *Current Top. Microbiol. Immunol.* **158**:1-24, 1992) and replication-deficient recombinant adenovirus (Berkner, *BioTechniques* **6**:616-629, 1988; Berkner, *Current Top. Microbiol. Immunol.* **158**:39-66, 1992; Brody and Crystal, *Annal. New York Acad. Sci.* **716**:90-103, 1994). Non-viral based vectors include protein/DNA complexes (Cristiano et al., *PNAS USA.* **90**:2122-2126, 1993; Curiel et al., *PNAS USA* **88**:8850-8854, 1991; Curiel, *Annal. New York Acad. Sci.* **716**:36-58, 1994), electroporation and liposome mediated delivery such as cationic liposomes (Farhood et al., *Annal. New York Acad. Sci.* **716**:23-35, 1994).

The present invention provides an improvement to the existing methods of expanding hematopoietic cells, into which new genetic material has been introduced, in that it provides methods utilizing G-CSF receptor agonists that may have improved biological activity and/or physical properties.

Determination of the Linker

The length of the amino acid sequence of the linker can be selected empirically or with guidance from structural information, or by using a combination of the two approaches.

When no structural information is available, a small series of linkers can be prepared for testing using a design whose length is varied in order to span a range from 0 to 50 Å and whose sequence is chosen in order to be consistent with surface exposure (hydrophilicity, Hopp & Woods, *Mol. Immunol.* **20**: 483-489, 1983; Kyte & Doolittle, *J. Mol. Biol.* **157**:105-132, 1982; solvent exposed surface area, Lee & Richards, *J. Mol. Biol.* **55**:379-400, 1971) and the ability to adopt the necessary conformation without deranging the configuration of the c-mpl receptor agonist (conformationally flexible; Karplus & Schulz, *Naturwissenschaften* **72**:212-213, (1985). Assuming an average of translation of 2.0 to 3.8 Å per residue, this would mean the length to test would be between 0 to 30 residues, with 0 to 15 residues being the preferred range. Exemplary of such an empirical series would be to construct linkers using a cassette sequence such as Gly-Gly-Gly-Ser (SEQ ID NO:2) repeated n times, where n is 1, 2, 3 or 4. Those skilled in the art will recognize that there are many such sequences that vary in length or composition that can serve as linkers with the primary consideration being that they be neither excessively long nor short (cf., Sandhu, *Critical Rev. Biotech.* **12**: 437-462, 1992); if they are too long, entropy effects will likely destabilize the three-dimensional fold, and may also make folding kinetically impractical, and if they are too short, they will likely destabilize the molecule because of torsional or steric strain.

Those skilled in the analysis of protein structural information will recognize that using the distance between the chain ends, defined as the distance between the c-alpha carbons, can be used to define the length of the sequence to be used, or at least to limit the number of possibilities that must be tested in an empirical selection of linkers. They will also recognize that it is sometimes the case that

the positions of the ends of the polypeptide chain are ill-defined in structural models derived from x-ray diffraction or nuclear magnetic resonance spectroscopy data, and that when true, this situation will therefore need to be taken into account in order to properly estimate the length of the linker required. From those residues whose positions are well defined are selected two residues that are close in sequence to the chain ends, and the distance between their c-alpha carbons is used to calculate an approximate length for a linker between them. Using the calculated length as a guide, linkers with a range of number of residues (calculated using 2 to 3.8Å per residue) are then selected. These linkers may be composed of the original sequence, shortened or lengthened as necessary, and when lengthened the additional residues may be chosen to be flexible and hydrophilic as described above; or optionally the original sequence may be substituted for using a series of linkers, one example being the Gly-Gly-Gly-Ser (SEQ ID NO:2) cassette approach mentioned above; or optionally a combination of the original sequence and new sequence having the appropriate total length may be used.

Determination of the Amino and Carboxyl Termini of G-CSF Receptor Agonists

Sequences of G-CSF receptor agonists capable of folding to biologically active states can be prepared by appropriate selection of the beginning (amino terminus) and ending (carboxyl terminus) positions from within the original polypeptide chain while using the linker sequence as described above. Amino and carboxyl termini are selected from within a common stretch of sequence, referred to as a breakpoint region, using the guidelines described below. A novel amino acid sequence is thus generated by selecting

amino and carboxyl termini from within the same breakpoint region. In many cases the selection of the new termini will be such that the original position of the carboxyl terminus immediately preceded that of the amino terminus. However, those skilled in the art will recognize that selections of termini anywhere within the region may function, and that these will effectively lead to either deletions or additions to the amino or carboxyl portions of the new sequence.

It is a central tenet of molecular biology that the primary amino acid sequence of a protein dictates folding to the three-dimensional structure necessary for expression of its biological function. Methods are known to those skilled in the art to obtain and interpret three-dimensional structural information using x-ray diffraction of single protein crystals or nuclear magnetic resonance spectroscopy of protein solutions. Examples of structural information that are relevant to the identification of breakpoint regions include the location and type of protein secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets, chain reversals and turns, and loops; Kabsch & Sander, *Biopolymers* **22**: 2577-2637, 1983; the degree of solvent exposure of amino acid residues, the extent and type of interactions of residues with one another (Chothia, *Ann. Rev. Biochem.* **53**:537-572; 1984) and the static and dynamic distribution of conformations along the polypeptide chain (Alber & Mathews, *Methods Enzymol.* **154**: 511-533, 1987). In some cases additional information is known about solvent exposure of residues; one example is a site of post-translational attachment of carbohydrate which is necessarily on the surface of the protein. When experimental structural information is not available, or is not feasible to obtain, methods are also available to analyze the primary amino acid sequence in order to make predictions of protein tertiary and secondary structure, solvent accessibility and the occurrence of turns and loops.

Biochemical methods are also sometimes applicable for empirically determining surface exposure when direct structural methods are not feasible; for example, using the identification of sites of chain scission following limited proteolysis in order to infer surface exposure (Gentile & Salvatore, *Eur. J. Biochem.* **218**:603-621, 1993)

Thus using either the experimentally derived structural information or predictive methods (e.g., Srinivisan & Rose *Proteins: Struct., Funct. & Genetics*, **22**: 81-99, 1995) the parental amino acid sequence is inspected to classify regions according to whether or not they are integral to the maintenance of secondary and tertiary structure. The occurrence of sequences within regions that are known to be involved in periodic secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets) are regions that should be avoided. Similarly, regions of amino acid sequence that are observed or predicted to have a low degree of solvent exposure are more likely to be part of the so-called hydrophobic core of the protein and should also be avoided for selection of amino and carboxyl termini. In contrast, those regions that are known or predicted to be in surface turns or loops, and especially those regions that are known not to be required for biological activity, are the preferred sites for location of the extremes of the polypeptide chain. Continuous stretches of amino acid sequence that are preferred based on the above criteria are referred to as a breakpoint region.

TABLE 1

OLIGONUCLEOTIDES

L-11start.seq	GCTCTGAGAG CCGCCAGAGC CGCCAGAGGG CTGCGCAAGG TGGCGTAGAA CGCG (SEQ ID NO:3)
L-11stop.seq	CAGCCCTCTG GCGGCTCTGG CGGCTCTCAG AGCTTCCTGC TCAAGTCTTT AGAG (SEQ ID NO:4)
BlstartP.seq	GGGCTGCGCA AGGTGGCG (SEQ ID NO:5)
blstopP.seq	ACACCATTGG GCCCTGCCAG C (SEQ ID NO:6)
39start.seq	GATCGACCAT GGCTTACAAG CTGTGCCACC CC (SEQ ID NO:7)
38stop.Seq	CGATCGAAGC TTATTAGGTG GCACACAGCT TCTCCT (SEQ ID NO:8)
97start.seq	GATCGACCAT GGCTCCCGAG TTGGGTCCCA CC (SEQ ID NO:9)
96stop.Seq	CGATCGAAGC TTATTAGGAT ATCCCTTCCA GGGCCT (SEQ ID NO:10)
126start.seq	GATCGACCAT GGCTATGGCC CCTGCCCTGC AG (SEQ ID NO:11)
125stop.Seq	CGATCGAAGC TTATTATCCC AGTTCTTCCA TCTGCT (SEQ ID NO:12)
133start.seq	GATCGACCAT GGCTACCCAG GGTGCCATGC CG (SEQ ID NO:13)
132stop.seq	CGATCGAAGC TTATTAGGGC TGCAGGGCAG GGGCCA (SEQ ID NO:14)
142start.seq	GATCGACCAT GGCTTCTGCT TTCCAGCGCC GG (SEQ ID NO:15)
141stop.Seq	CGATCGAAGC TTATTAGGCG AAGGCCGGCA TGGCAC (SEQ ID NO:16)
96for.Seq	ATATCCATGG CTCCGGAACT GGGTCCAACT CTG (SEQ ID NO:17)
96rev.Seq	ACCTCCAGGA AGCTCTGCAG ATGG (SEQ ID NO:18)

125for.seq TATATCCATG GCTATGGCTC CAGCTCTGCA ACCAACTCAA GGTGCAATGC CAGCATTTGC ATCTG (SEQ ID NO:19)

125rev.seq GATGGCTAGC AACCAGAACA CCACCTGCAC GACGTTGAAA AGCAGATGCA AATGCTGGCA TTG (SEQ ID NO:20)

132for.seq TATATCCATG GCTACTCAAG GTGCTATGCC AGCTTTTGCT TCTGCTTTTC AACGTCG (SEQ ID NO:21)

132rev.seq GCAGATGGCT AGCAACCAGA ACACCACCTG CACGACGTTG AAAAGCAGAA GCAAAAGC (SEQ ID NO:22)

141for.seq CATGGCTTCT GCTTTTCAAC GTCGTGCAGG TGGTGTTCTG GTTG (SEQ ID NO:23)

141rev.seq CTAGCAACCA GAACACCACC TGCACGACGT TGAAAAGCAG AAGC (SEQ ID NO:24)

49start.seq GATCGACCAT GGCTCTGCTC GGACACTCTC TG (SEQ ID NO:68)

48stop.seq CGATCGAAGC TTATTACACC AGCTCCTCGG GGTGGC (SEQ ID NO:69)

77start.seq GATCGACCAT GGCTCAACTC CATAGCGGCC TT (SEQ ID NO:70)

76stop.seq CGATCGAAGC TTATTAGCTC AAGCAGCCTG CCAGCT (SEQ ID NO:71)

82start.seq GATCGACCAT GGCTCTTTTC CTCTACCAGG GG (SEQ ID NO:72)

81stop.seq CGATCGAAGC TTATTAGCCG CTATGGAGTT GGCTCA (SEQ ID NO:73)

84start.seq GATCGACCAT GGCTCTCTAC CAGGGGCTCC TG (SEQ ID NO:74)

83stop.seq CGATCGAAGC TTATTAGAAA AGGCCGCTAT GGAGTT (SEQ ID NO:75)

91start.seq GATCGACCAT GGCTGCCCTG GAAGGGATAT CC (SEQ ID NO:76)

90stop.seq CGATCGAAGC TTATTACTGC AGGAGCCCCT GGTAGA (SEQ ID NO:77)

112start.seq	GATCGACCAT GGCTGACTTT GCCACCACCA TC (SEQ ID NO:78)
111stop.seq	CGATCGAAGC TTATTAGGCG ACGTCCAGCT GCAGTG (SEQ ID NO:79)
117start.seq	GATCGACCAT GGCTATCTGG CAGCAGATGG AA (SEQ ID NO:80)
116stop.seq	CGATCGAAGC TTATTAGGTG GTGGCAAAGT CGGCGA (SEQ ID NO:81)
119start.seq	GATCGACCAT GGCTCAGCAG ATGGAAGAAC TG (SEQ ID NO:82)
118stop.seq	CGATCGAAGC TTATTACCAG ATGGTGGTGG CAAAGT (SEQ ID NO:83)
Z4849at.for	CATGGCTTTG TTAGGACATT CTTTAGGTAT TCCATGGGCT CCTCTGAGCT (SEQ ID NO:84)
Z4849at.rev	CAGAGGAGCC CATGGAATAC CTAAAGAATG TCCTAACAAA GC (SEQ ID NO:85)

TABLE 2

DNA sequences

pMON3485.Seq

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  1  ATGGCTTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC
 51  TCTGGGCATC CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC
101  AGCTGGCAGG CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG
151  GGGCTCCTGC AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT
201  GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC
251  AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
301  ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT
351  TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC
401  ACCTTGCGCA GCCCTCTGGC GGCTCTGGCG GCTCTCAGAG CTTCCTGCTC
451  AAGTCTTTAG AGCAAGTGAG GAAGATCCAG GGCGATGGCG CAGCGCTCCA
501  GGAGAAGCTG TGTGCCACCT AATAA (SEQ ID NO:25)
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pMON3486.Seq

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  1  ATGGCTCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC
 51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
201  GGAGGCGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC TCTGGCGGCT
251  CTGGCGGCTC TCAGAGCTTC CTGCTCAAGT CTTTAGAGCA AGTGAGGAAG
301  ATCCAGGGCG ATGGCGCAGC GCTCCAGGAG AAGCTGTGTG CCACCTACAA
351  GCTGTGCCAC CCCGAGGAGC TGGTGCTGCT CGGACACTCT CTGGGCATCC
401  CCTGGGCTCC CCTGAGCTCC TGCCCCAGCC AGGCCCTGCA GCTGGCAGGC
451  TGCTTGAGCC AACTCCATAG CGGCCTTTTC CTCTACCAGG GGCTCCTGCA
501  GGCCCTGGAA GGGATATCCT AATAA (SEQ ID NO:26)
```

pMON3487.Seq

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  1  ATGGCTATGG CCCCTGCCCT GCAGCCCACC CAGGGTGCCA TGCCGGCCTT
 51  CGCCTCTGCT TTCCAGCGCC GGGCAGGAGG GGTCCTGGTT GCTAGCCATC
101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
151  CCCTCTGGCG GCTCTGGCGG CTCTCAGAGC TTCCTGCTCA AGTCTTTAGA
201  GCAAGTGAGG AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT
251  GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGCT GCTCGGACAC
301  TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT
351  GCAGCTGGCA GGCTGCTTGA GCCAACTCCA TAGCGGCCTT TTCCTCTACC
401  AGGGGCTCCT GCAGGCCCTG GAAGGGATAT CCCCCGAGTT GGGTCCCACC
451  TTGGACACAC TGCAGCTGGA CGTCGCCGAC TTTGCCACCA CCATCTGGCA
501  GCAGATGGAA GAACTGGGAT AATAA (SEQ ID NO:27)
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pMON3488.Seq

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  1  ATGGCTACCC AGGGTGCCAT GCCGGCCTTC GCCTCTGCTT TCCAGCGCCG
 51  GGCAGGAGGG GTCCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCTCTGGCGG CTCTGGCGGC
151  TCTCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGGA AGATCCAGGG
201  CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAC AAGCTGTGCC
251  ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
301  CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG
351  CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG
401  AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
451  GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT
501  GGCCCCTGCC CTGCAGCCCT AATAA (SEQ ID NO:28)
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pMON3489.Seq

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  1  ATGGCTTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA
 51  TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCTCTGG CGGCTCTGGC GGCTCTCAGA GCTTCCTGCT CAAGTCTTTA
151  GAGCAAGTGA GGAAGATCCA GGGCGATGGC GCAGCGCTCC AGGAGAAGCT
201  GTGTGCCACC TACAAGCTGT GCCACCCCGA GGAGCTGGTG CTGCTCGGAC
251  ACTCTCTGGG CATCCCCTGG GCTCCCCTGA GCTCCTGCCC CAGCCAGGCC
301  CTGCAGCTGG CAGGCTGCTT GAGCCAACTC CATAGCGGCC TTTTCCTCTA
351  CCAGGGGCTC CTGCAGGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA
401  CCTTGGACAC ACTGCAGCTG GACGTCGCCG ACTTTGCCAC CACCATCTGG
451  CAGCAGATGG AAGAACTGGG AATGGCCCCT GCCCTGCAGC CCACCCAGGG
501  TGCCATGCCG GCCTTCGCCT AATAA  (SEQ ID NO:29)
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pMON3490.seq

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  1  ATGGCTTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC
 51  TCTGGGCATC CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC
101  AGCTGGCAGG CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG
151  GGGCTCCTGC AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT
201  GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC
251  AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
301  ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT
351  TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC
401  ACCTTGCGCA GCCCACACCA TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC
451  TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG GCGATGGCGC
501  AGCGCTCCAG GAGAAGCTGT GTGCCACCTA ATAA  (SEQ ID NO:30)
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pMON3491.seq

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  1  ATGGCTCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC
 51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC ACACCATTGG
251  GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
301  GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC
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351  CACCTACAAG CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC
401  TGGGCATCCC CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG
451  CTGGCAGGCT GCTTGAGCCA ACTCCATAGC GGCCTTTTCC TCTACCAGGG
501  GCTCCTGCAG GCCCTGGAAG GGATATCCTA ATAA (SEQ ID NO:31)
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pMON3492.seq

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  1  ATGGCTATGG CCCCTGCCCT GCAGCCCACC CAGGGTGCCA TGCCGGCCTT
 51  CGCCTCTGCT TTCCAGCGCC GGGCAGGAGG GGTCCTGGTT GCTAGCCATC
101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
151  CCCACACCAT TGGGCCCTGC CAGCTCCCTG CCCCAGAGCT TCCTGCTCAA
201  GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA GCGCTCCAGG
251  AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
301  CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG
351  CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT
401  TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
451  GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC
501  CATCTGGCAG CAGATGGAAG AACTGGGATA ATAA (SEQ ID NO:32)
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pMON3493.seq

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  1  ATGGCTACCC AGGGTGCCAT GCCGGCCTTC GCCTCTGCTT TCCAGCGCCG
 51  GGCAGGAGGG GTCCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCACACCATT GGGCCCTGCC
151  AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG TCTTTAGAGC AAGTGAGAAA
201  GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT GCCACCTACA
251  AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
301  CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG
351  CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC
401  AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
451  CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA
501  ACTGGGAATG GCCCCTGCCC TGCAGCCCTA ATAA  (SEQ ID NO:33)
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pMON3494.seq

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  1  ATGGCTTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA
 51  TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCACACC ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC
151  AAGTCTTTAG AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA
201  GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC
251  TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
301  AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT
351  TTTCCTCTAC CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT
401  TGGGTCCCAC CTTGGACACA CTGCAGCTGG ACGTCGCCGA CTTTGCCACC
451  ACCATCTGGC AGCAGATGGA AGAACTGGGA ATGGCCCCTG CCCTGCAGCC
501  CACCCAGGGT GCCATGCCGG CCTTCGCCTA ATAA  (SEQ ID NO:34)
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pMON25181.seq

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  1  ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC
 51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC ACACCATTGG
251  GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
301  GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC
351  CACCTACAAG CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC
401  TGGGCATCCC CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG
451  CTGGCAGGCT GCTTGAGCCA ACTCCATAGC GGCCTTTTCC TCTACCAGGG
501  GCTCCTGCAG GCCCTGGAAG GGATATCCTA A  (SEQ ID NO:35)
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pMON25182.seq

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  1  ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT
 51  TGCATCTGCT TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC
101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
151  CCCACACCAT TGGGCCCTGC CAGCTCCCTG CCCCAGAGCT TCCTGCTCAA
201  GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA GCGCTCCAGG
251  AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
301  CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG
351  CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT
401  TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
451  GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC
501  CATCTGGCAG CAGATGGAAG AACTGGGATA A (SEQ ID NO:36)
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pMON25183.seq

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  1  ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG
 51  TGCAGGTGGT GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCACACCATT GGGCCCTGCC
151  AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG TCTTTAGAGC AAGTGAGAAA
201  GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT GCCACCTACA
251  AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
301  CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG
351  CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC
401  AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
451  CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA
501  ACTGGGAATG GCCCCTGCCC TGCAGCCCTA A (SEQ ID NO:37)
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pMON25184.seq

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  1  ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA
 51  TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCACACC ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC
151  AAGTCTTTAG AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA
201  GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC
251  TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
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 301  AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT
 351  TTTCCTCTAC CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT
 401  TGGGTCCCAC CTTGGACACA CTGCAGCTGG ACGTCGCCGA CTTTGCCACC
 451  ACCATCTGGC AGCAGATGGA AGAACTGGGA ATGGCCCCTG CCCTGCAGCC
 501  CACCCAGGGT GCCATGCCGG CCTTCGCCTA A (SEQ ID NO:38)
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pMON25185.seq

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   1  ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC
  51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
 101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
 151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
 201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC TCTGGCGGCT
 251  CTGGCGGCTC TCAGAGCTTC CTGCTCAAGT CTTTAGAGCA AGTGAGAAAG
 301  ATCCAGGGCG ATGGCGCAGC GCTCCAGGAG AAGCTGTGTG CCACCTACAA
 351  GCTGTGCCAC CCCGAGGAGC TGGTGCTGCT CGGACACTCT CTGGGCATCC
 401  CCTGGGCTCC CCTGAGCTCC TGCCCCAGCC AGGCCCTGCA GCTGGCAGGC
 451  TGCTTGAGCC AACTCCATAG CGGCCTTTTC CTCTACCAGG GGCTCCTGCA
 501  GGCCCTGGAA GGGATATCCT AA (SEQ ID NO:39)
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pMON25186.seq

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   1  ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT
  51  TGCATCTGCT TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC
 101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
 151  CCCTCTGGCG GCTCTGGCGG CTCTCAGAGC TTCCTGCTCA AGTCTTTAGA
 201  GCAAGTGAGA AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT
 251  GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGCT GCTCGGACAC
 301  TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT
 351  GCAGCTGGCA GGCTGCTTGA GCCAACTCCA TAGCGGCCTT TTCCTCTACC
 401  AGGGGCTCCT GCAGGCCCTG GAAGGGATAT CCCCCGAGTT GGGTCCCACC
 451  TTGGACACAC TGCAGCTGGA CGTCGCCGAC TTTGCCACCA CCATCTGGCA
 501  GCAGATGGAA GAACTGGGAT AA (SEQ ID NO:40)
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pMON25187.seq

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   1  ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG
  51  TGCAGGTGGT GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
 101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCTCTGGCGG CTCTGGCGGC
 151  TCTCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGAA AGATCCAGGG
 201  CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAC AAGCTGTGCC
 251  ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
 301  CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG
 351  CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG
 401  AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
 451  GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT
 501  GGCCCCTGCC CTGCAGCCCT AA  (SEQ ID NO:41)
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pMON25188.seq

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  1  ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA
 51  TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCTCTGG CGGCTCTGGC GGCTCTCAGA GCTTCCTGCT CAAGTCTTTA
151  GAGCAAGTGA GAAAGATCCA GGGCGATGGC GCAGCGCTCC AGGAGAAGCT
201  GTGTGCCACC TACAAGCTGT GCCACCCCGA GGAGCTGGTG CTGCTCGGAC
251  ACTCTCTGGG CATCCCCTGG GCTCCCCTGA GCTCCTGCCC CAGCCAGGCC
301  CTGCAGCTGG CAGGCTGCTT GAGCCAACTC CATAGCGGCC TTTTCCTCTA
351  CCAGGAGCTC CTGCAGGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA
401  CCTTGGACAC ACTGCAGCTG GACGTCGCCG ACTTTGCCAC CACCATCTGG
451  CAGCAGATGG AAGAACTGGG AATGGCCCCT GCCCTGCAGC CCACCCAGGG
501  TGCCATGCCG GCCTTCGCCT AA (SEQ ID NO:42)
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pMON3460.seq

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  1  ATGGCTCTGC TCGGACACTC TCTGGGCATC CCCTGGGCTC CCCTGAGCTC
 51  CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC CAACTCCATA
101  GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
151  CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT
201  TGCCACCACC ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC
251  TGCAGCCCAC CCAGGGTGCC ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC
301  CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT
351  GTCGTACCGC GTTCTACGCC ACCTTGCGCA GCCCACACCA TTGGGCCCTG
401  CCAGCTCCCT GCCCCAGAGC TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA
451  AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA
501  CAAGCTGTGC CACCCCGAGG AGCTGGTGTA ATAA (SEQ ID NO:86)
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pMON3461.seq

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  1  ATGGCTCAAC TCCATAGCGG CCTTTTCCTC TACCAGGGGC TCCTGCAGGC
 51  CCTGGAAGGG ATATCCCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC
101  TGGACGTCGC CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG
151  GGAATGGCCC CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC
201  CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC
251  AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
301  ACACCATTGG GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC
351  TTTAGAGCAA GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA
401  AGCTGTGTGC CACCTACAAG CTGTGCCACC CCGAGGAGCT GGTGCTGCTC
451  GGACACTCTC TGGGCATCCC CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA
501  GGCCCTGCAG CTGGCAGGCT GCTTGAGCTA ATAA (SEQ ID NO:87)
```

pMON3462.seq

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  1  ATGGCTCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC
 51  CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT
101  TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT GGCCCCTGCC
151  CTGCAGCCCA CCCAGGGTGC CATGCCGGCC TTCGCCTCTG CTTTCCAGCG
201  CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC TTCCTGGAGG
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251  TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCACACC ATTGGGCCCT
301  GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC AAGTCTTTAG AGCAAGTGAG
351  AAAGATCCAG GGCGATGGCG CAGCGCTCCA GGAGAAGCTG TGTGCCACCT
401  ACAAGCTGTG CCACCCCGAG GAGCTGGTGC TGCTCGGACA CTCTCTGGGC
451  ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC AGCCAGGCCC TGCAGCTGGC
501  AGGCTGCTTG AGCCAACTCC ATAGCGGCTA ATAA (SEQ ID NO:88)
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pMON3463.seq

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  1  ATGGCTCTCT ACCAGGGGCT CCTGCAGGCC CTGGAAGGGA TATCCCCCGA
 51  GTTGGGTCCC ACCTTGGACA CACTGCAGCT GGACGTCGCC GACTTTGCCA
101  CCACCATCTG GCAGCAGATG GAAGAACTGG GAATGGCCCC TGCCCTGCAG
151  CCCACCCAGG GTGCCATGCC GGCCTTCGCC TCTGCTTTCC AGCGCCGGGC
201  AGGAGGGGTC CTGGTTGCTA GCCATCTGCA GAGCTTCCTG GAGGTGTCGT
251  ACCGCGTTCT ACGCCACCTT GCGCAGCCCA CACCATTGGG CCCTGCCAGC
301  TCCCTGCCCC AGAGCTTCCT GCTCAAGTCT TTAGAGCAAG TGAGAAAGAT
351  CCAGGGCGAT GGCGCAGCGC TCCAGGAGAA GCTGTGTGCC ACCTACAAGC
401  TGTGCCACCC CGAGGAGCTG GTGCTGCTCG GACACTCTCT GGGCATCCCC
451  TGGGCTCCCC TGAGCTCCTG CCCCAGCCAG GCCCTGCAGC TGGCAGGCTG
501  CTTGAGCCAA CTCCATAGCG GCCTTTTCTA ATAA (SEQ ID NO:89)
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pMON3464.seq

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 51  ACTGCAGCTG GACGTCGCCG ACTTTGCCAC CACCATCTGG CAGCAGATGG
101  AAGAACTGGG AATGGCCCCT GCCCTGCAGC CCACCCAGGG TGCCATGCCG
151  GCCTTCGCCT CTGCTTTCCA GCGCCGGGCA GGAGGGGTCC TGGTTGCTAG
201  CCATCTGCAG AGCTTCCTGG AGGTGTCGTA CCGCGTTCTA CGCCACCTTG
251  CGCAGCCCAC ACCATTGGGC CCTGCCAGCT CCCTGCCCCA GAGCTTCCTG
301  CTCAAGTCTT TAGAGCAAGT GAGAAAGATC CAGGGCGATG GCGCAGCGCT
351  CCAGGAGAAG CTGTGTGCCA CCTACAAGCT GTGCCACCCC GAGGAGCTGG
401  TGCTGCTCGG ACACTCTCTG GGCATCCCCT GGGCTCCCCT GAGCTCCTGC
451  CCCAGCCAGG CCCTGCAGCT GGCAGGCTGC TTGAGCCAAC TCCATAGCGG
501  CCTTTTCCTC TACCAGGGGC TCCTGCAGTA ATAA (SEQ ID NO:90)
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pMON3465.seq

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  1  ATGGCTGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT
 51  GGCCC TGCC CTGCAGCCCA CCCAGGGTGC CATGCCGGCC TTCGCCTCTG
101  CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC
151  TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCACACC
201  ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC AAGTCTTTAG
251  AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA GGAGAAGCTG
301  TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC TGCTCGGACA
351  CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC AGCCAGGCCC
401  TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT TTTCCTCTAC
451  CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT TGGGTCCCAC
501  CTTGGACACA CTGCAGCTGG ACGTCGCCTA ATAA (SEQ ID NO:91)
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pMON 3466.seq

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  1  ATGGCTATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA
 51  GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG
101  CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT GGAGGTGTCG
151  TACCGCGTTC TACGCCACCT TGCGCAGCCC ACACCATTGG GCCCTGCCAG
201  CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA GTGAGAAAGA
251  TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC CACCTACAAG
301  CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC TGGGCATCCC
351  CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG CTGGCAGGCT
401  GCTTGAGCCA ACTCCATAGC GGCCTTTTCC TCTACCAGGG GCTCCTGCAG
451  GCCCTGGAAG GGATATCCCC CGAGTTGGGT CCCACCTTGG ACACACTGCA
501  GCTGGACGTC GCCGACTTTG CCACCACCTA ATAA (SEQ ID NO:92)
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pMON3467.seq

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  1  ATGGCTCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC
 51  CCAGGGTGCC ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG
101  GGGTCCTGGT TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC
151  GTTCTACGCC ACCTTGCGCA GCCCACACCA TTGGGCCCTG CCAGCTCCCT
201  GCCCCAGAGC TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG
251  GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA CAAGCTGTGC
301  CACCCCGAGG AGCTGGTGCT GCTCGGACAC TCTCTGGGCA TCCCCTGGGC
351  TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT GCAGCTGGCA GGCTGCTTGA
401  GCCAACTCCA TAGCGGCCTT TTCCTCTACC AGGGGCTCCT GCAGGCCCTG
451  GAAGGGATAT CCCCCGAGTT GGGTCCCACC TTGGACACAC TGCAGCTGGA
501  CGTCGCCGAC TTTGCCACCA CCATCTGGTA ATAA (SEQ ID NO:93)
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pMON3499.seq

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  1  ATGGCTTTGT TAGGACATTC TTTAGGTATT CCATGGGCTC CTCTGAGCTC
 51  CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC CAACTCCATA
101  GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
151  CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT
201  TGCCACCACC ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC
251  TGCAGCCCAC CCAGGGTGCC ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC
301  CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT
351  GTCGTACCGC GTTCTACGCC ACCTTGCGCA GCCCACACCA TTGGGCCCTG
401  CCAGCTCCCT GCCCCAGAGC TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA
451  AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA
501  CAAGCTGTGC CACCCCGAGG AGCTGGTGTA ATAA  (SEQ ID NO:94)
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TABLE 3

PROTEIN SEQUENCES

pMON3485.Pep

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala
Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe
Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln
Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser
Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln
Glu Lys Leu Cys Ala Thr (SEQ ID NO:43)

pMON3486.Pep

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
Ala Leu Glu Gly Ile Ser (SEQ ID NO:44)

pMON3487.Pep

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro
Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala
Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys
Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu
Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp
Gln Met Glu Glu Leu Gly (SEQ ID NO:45)

pMON3488.Pep

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly
Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys
Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly
His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro (SEQ ID NO:46)

pMON3489.Pep

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
Ala Met Pro Ala Phe Ala (SEQ ID NO:47)

pMON3490.Pep

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala
Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe
Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln
Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:48)

pMON3491.Pep

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:49)

pMON3492.Pep

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln
Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly
Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu
Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile
Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro
Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr
Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:50)

pMON3493.Pep

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu
Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:51)

pMON3494.Pep

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val L u Leu Gly His Ser-Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala

Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile
Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:52)

pMON25181.pep

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:53)

pMON25182.pep

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln
Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly
Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu
Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile
Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro
Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr
Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:54)

pMON25183.pep

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu
Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:55)

pMON25184.pep

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile
Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:56)

pMON25185.pep

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
Ala Leu Glu Gly Ile Ser (SEQ ID NO:57)

pMON25186.pep

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu
Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu
Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser
Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala
Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu
Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met
Glu Glu Leu Gly (SEQ ID NO:58)

pMON25187.pep

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly
Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys
Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly
His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro (SEQ ID NO:59)

pMON25188.pep

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
Ala Met Pro Ala Phe Ala (SEQ ID NO:60)

pMON3460.Pep

Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro
Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val
Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu
Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu
Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile
Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
Lys Leu Cys His Pro Glu Glu Leu Val (SEQ ID NO:95)

pMON3461.Pep

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala
Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu
Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met

Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala
Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg
Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser
Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg
Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala
Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His
Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln
Ala Leu Gln Leu Ala Gly Cys Leu Ser (SEQ ID NO:96)

3462.Pep

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly (SEQ ID NO:97)

3463.Pep

Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln
Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro
Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala
Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys
Leu Ser Gln Leu His Ser Gly Leu Phe (SEQ ID NO:98)

3464.Pep

Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr
Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala
Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val

Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys
Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly
His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
Leu Phe Leu Tyr Gln Gly Leu Leu Gln (SEQ ID NO:99)

3465.Pep

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
Leu Asp Thr Leu Gln Leu Asp Val Ala (SEQ ID NO:100)

3466.Pep

Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln
Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg
Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu
Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro
Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser
Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln
Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser
Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln
Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu
Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln
Leu Asp Val Ala Asp Phe Ala Thr Thr (SEQ ID NO:101)

3467.Pep

Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr
Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val
Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly
Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu
Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu
Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys
Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly
Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp

Val Ala Asp Phe Ala Thr Thr Ile Trp (SEQ ID NO:102)

3499.Pep

Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro
Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val
Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu
Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu
Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile
Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
Lys Leu Cys His Pro Glu Glu Leu Val (SEQ ID NO:103)

Materials and Methods

Recombinant DNA methods

Unless noted otherwise, all specialty chemicals were obtained from Sigma Co., (St. Louis, MO). Restriction endonucleases and T4 DNA ligase were obtained from New England Biolabs (Beverly, MA) or Boehringer Mannheim (Indianapolis, IN).

Transformation of *E. coli* strains

E. coli strains, such as DH5α™ (Life Technologies, Gaithersburg, MD) and TG1 (Amersham Corp., Arlington Heights, IL) are used for transformation of ligation reactions and are the source of plasmid DNA for transfecting mammalian cells. *E. coli* strains, such as MON105 and JM101, can be used for expressing the G-CSF receptor agonist of the present invention in the cytoplasm or periplasmic space.

MON105 ATCC#55204: F-, lamda-,IN(rrnD, rrE)1, rpoD+, rpoH358

DH5α™: F-, phi80dlacZdeltaM15, delta(lacZYA-argF)U169, deoR, recA1, endA1, hsdR17(rk-,mk+), phoA, supE44lamda-, thi-1, gyrA96, relA1

TG1: delta(lac-pro), supE, thi-1, hsdD5/F'(traD36, proA+B+, lacIq, lacZdeltaM15)

DH5α™ Subcloning efficiency cells are purchased as competent cells and are ready for transformation using the manufacturer's protocol, while both *E. coli* strains TG1 and MON105 are rendered competent to take up DNA using a $CaCl_2$ method. Typically, 20 to 50 mL of cells are grown in LB medium (1% Bacto-tryptone, 0.5% Bacto-yeast extract, 150 mM

NaCl) to a density of approximately 1.0 optical density unit at 600 nanometers (OD600) as measured by a Baush & Lomb Spectronic spectrophotometer (Rochester, NY). The cells are collected by centrifugation and resuspended in one-fifth culture volume of $CaCl_2$ solution (50 mM $CaCl_2$, 10 mM Tris-Cl, pH7.4) and are held at 4°C for 30 minutes. The cells are again collected by centrifugation and resuspended in one-tenth culture volume of $CaCl_2$ solution. Ligated DNA is added to 0.2mL of these cells, and the samples are held at 4°C for 1 hour. The samples are shifted to 42°C for two minutes and 1mL of LB is added prior to shaking the samples at 37°C for one hour. Cells from these samples are spread on plates (LB medium plus 1.5% Bacto-agar) containing either ampicillin (100 micrograms/mL, ug/mL) when selecting for ampicillin-resistant transformants, or spectinomycin (75 ug/mL) when selecting for spectinomycin-resistant transformants. The plates are incubated overnight at 37°C. Single colonies are picked, grown in LB supplemented with appropriate antibiotic for 6-16 hours at 37°C with shaking.

Colonies are picked and inoculated into LB plus appropriate antibiotic (100 ug/mL ampicillin or 75 ug/mL spectinomycin) and are grown at 37°C while shaking. Before harvesting the cultures, 1 ul of cells are analyzed by PCR for the presence of a G-CSF gene. The PCR is carried out using a combination of primers that anneal to the G-CSF gene and/or vector. After the PCR is complete, loading dye is added to the sample followed by electrophoresis as described earlier. A gene has been ligated to the vector when a PCR product of the expected size is observed.

Methods for creation of genes with new N-terminus/C-terminus

Method I. Creation of genes with new N-terminus/C-terminus which contain a linker region.

Genes with new N-terminus/C-terminus which contain a linker region separating the original C-terminus and N-terminus can be made essentially following the method described in L. S. Mullins, et al *J. Am. Chem. Soc.* **116**, 5529-5533 (1994). Multiple steps of polymerase chain reaction (PCR) amplifications are used to rearrange the DNA sequence encoding the primary amino acid sequence of the protein. The steps are illustrated in Figure 2.

In the first step, the primer set ("new start" and "linker start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein followed by the linker that connects the C-terminal and N-terminal ends of the original protein. In the second step, the primer set ("new stop" and "linker stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that encodes the same linker as used above, followed by the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include the appropriate restriction enzyme recognition sites which allow cloning of the new gene into expression plasmids. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT).

"Fragment Start" and "Fragment Stop", which have complementary sequence in the linker region and the coding sequence for the two amino acids on both sides of the linker, are joined together in a third PCR step to make the full-length gene encoding the new protein. The DNA fragments "Fragment Start" and "Fragment Stop" are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined in equimolar quantities, heated at 70°C for ten minutes and slow cooled to allow annealing through their shared sequence in "linker start" and "linker stop". In the third PCR step, primers "new start" and "new stop" are added to the annealed fragments to create and amplify the full-length new N-terminus/C-terminus gene. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 60°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and approximately 0.5 ug of DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are purified using a Wizard PCR Preps kit (Promega).

Method II. Creation of genes with new N-terminus/C-terminus without a linker region.

New N-terminus/C-terminus genes without a linker joining the original N-terminus and C-terminus can be made using two steps of PCR amplification and a blunt end ligation. The steps are illustrated in Figure 3. In the first step, the primer set ("new start" and "P-bl start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the

sequence encoding the new N-terminal portion of the new protein. In the second step, the primer set ("new stop" and "P-bl stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that contains the sequence encoding the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include appropriate restriction sites which allow cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for 45 seconds and 72°C extension for 45 seconds. Deep Vent polymerase (New England Biolabs) is used to reduce the occurrence of overhangs in conditions recommended by the manufacturer. The "P-bl start" and "P-bl stop" primers are phosphorylated at the 5' end to aid in the subsequent blunt end ligation of "Fragment Start" and "Fragment Stop" to each other. A 100 ul reaction contained 150 pmole of each primer and one ug of template DNA; and 1x Vent buffer (New England Biolabs), 300 uM dGTP, 300 uM dATP, 300 uM dTTP, 300 uM dCTP, and 1 unit Deep Vent polymerase. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reaction products are purified using a Wizard PCR Preps kit (Promega).

The primers are designed to include appropriate restriction enzyme recognition sites which allow for the cloning of the new gene into expression vectors. Typically "Fragment Start" is designed to create a NcoI restriction site , and "Fragment Stop" is designed to create a HindIII restriction site. Restriction digest reactions are purified using a Magic DNA Clean-up System kit (Promega). Fragments Start and Stop are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined with and

annealed to the ends of the ~ 3800 base pair NcoI/HindIII vector fragment of pMON3934 by heating at 50°C for ten minutes and allowed to slow cool. The three fragments are ligated together using T4 DNA ligase (Boehringer Mannheim). The result is a plasmid containing the full-length new N-terminus/C-terminus gene. A portion of the ligation reaction is used to transform *E. coli* strain DH5αcells (Life Technologies, Gaithersburg, MD). Plasmid DNA is purified and sequence confirmed as below.

Method III. Creation of new N-terminus/C-terminus genes by tandem-duplication method

New N-terminus/C-terminus genes can be made based on the method described in R. A. Horlick, et al *Protein Eng.* 5:427-431 (1992). Polymerase chain reaction (PCR) amplification of the new N-terminus/C-terminus genes is performed using a tandemly duplicated template DNA. The steps are illustrated in Figure 4.

The tandemly-duplicated template DNA is created by cloning and contains two copies of the gene separated by DNA sequence encoding a linker connecting the original C- and N-terminal ends of the two copies of the gene. Specific primer sets are used to create and amplify a full-length new N terminus/C-terminus gene from the tandemly-duplicated template DNA. These primers are designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit (Perkin Elmer Corporation, Norwalk, CT) is used. A 100 ul reaction contains 100 pmole of each primer

and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reactions are purified using a Wizard PCR Preps kit (Promega).

DNA isolation and characterization

Plasmid DNA can be isolated by a number of different methods and using commercially available kits known to those skilled in the art. A few such methods are shown herein. Plasmid DNA is isolated using the Promega Wizard™ Miniprep kit (Madison, WI), the Qiagen QIAwell Plasmid isolation kits (Chatsworth, CA) or Qiagen Plasmid Midi kit. These kits follow the same general procedure for plasmid DNA isolation. Briefly, cells are pelleted by centrifugation (5000 x g), plasmid DNA released with sequential NaOH/acid treatment, and cellular debris is removed by centrifugation (10000 x g). The supernatant (containing the plasmid DNA) is loaded onto a column containing a DNA-binding resin, the column is washed, and plasmid DNA eluted with TE. After screening for the colonies with the plasmid of interest, the *E. coli* cells are inoculated into 50-100 mLs of LB plus appropriate antibiotic for overnight growth at 37°C in an air incubator while shaking. The purified plasmid DNA is used for DNA sequencing, further restriction enzyme digestion, additional subcloning of DNA fragments and transfection into mammalian, *E. coli* or other cells.

Sequence confirmation.

Purified plasmid DNA is resuspended in dH_2O and quantitated by measuring the absorbance at 260/280 nm in a Bausch and Lomb Spectronic 601 UV spectrometer. DNA samples are sequenced using ABI PRISM™ DyeDeoxy™ terminator

sequencing chemistry (Applied Biosystems Division of Perkin Elmer Corporation, Lincoln City, CA) kits (Part Number 401388 or 402078) according to the manufacturers suggested protocol usually modified by the addition of 5% DMSO to the sequencing mixture. Sequencing reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT) following the recommended amplification conditions. Samples are purified to remove excess dye terminators with Centri-Sep™ spin columns (Princeton Separations, Adelphia, NJ) and lyophilized. Fluorescent dye labeled sequencing reactions are resuspended in deionized formamide, and sequenced on denaturing 4.75% polyacrylamide-8M urea gels using an ABI Model 373A automated DNA sequencer. Overlapping DNA sequence fragments are analyzed and assembled into master DNA contigs using Sequencher v2.1 DNA analysis software (Gene Codes Corporation, Ann Arbor, MI).

Expression of G-CSF receptor agonists in mammalian cells

Mammalian Cell Transfection/Production of Conditioned Media

The BHK-21 cell line can be obtained from the ATCC (Rockville, MD). The cells are cultured in Dulbecco's modified Eagle media (DMEM/high-glucose), supplemented to 2mM (mM) L-glutamine and 10% fetal bovine serum (FBS). This formulation is designated BHK growth media. Selective media is BHK growth media supplemented with 453 units/mL hygromycin B (Calbiochem, San Diego, CA). The BHK-21 cell line was previously stably transfected with the HSV transactivating protein VP16, which transactivates the IE110 promoter found on the plasmid pMON3359 (See Hippenmeyer et al., *Bio/Technology*, pp.1037-1041, 1993). The VP16 protein drives expression of genes inserted behind the IE110 promoter. BHK-21 cells expressing the transactivating

protein VP16 are designated BHK-VP16. The plasmid pMON1118 (See Highkin et al., *Poultry Sci.*, **70**: 970-981, 1991) expresses the hygromycin resistance gene from the SV40 promoter. A similar plasmid is available from ATCC, pSV2-hph.

BHK-VP16 cells are seeded into a 60 millimeter (mm) tissue culture dish at 3 X 10^5 cells per dish 24 hours prior to transfection. Cells are transfected for 16 hours in 3 mL of "OPTIMEM"™ (Gibco-BRL, Gaithersburg, MD) containing 10 ug of plasmid DNA containing the gene of interest, 3 ug hygromycin resistance plasmid, pMON1118, and 80 ug of Gibco-BRL "LIPOFECTAMINE"™ per dish. The media is subsequently aspirated and replaced with 3 mL of growth media. At 48 hours post-transfection, media from each dish is collected and assayed for activity (transient conditioned media). The cells are removed from the dish by trypsin-EDTA, diluted 1:10 and transferred to 100 mm tissue culture dishes containing 10 mL of selective media. After approximately 7 days in selective media, resistant cells grow into colonies several millimeters in diameter. The colonies are removed from the dish with filter paper (cut to approximately the same size as the colonies and soaked in trypsin/EDTA) and transferred to individual wells of a 24 well plate containing 1 mL of selective media. After the clones are grown to confluence, the conditioned media is re-assayed, and positive clones are expanded into growth media.

Expression of G-CSF receptor agonists in *E. coli*

E. coli strain MON105 or JM101 harboring the plasmid of interest are grown at 37°C in M9 plus casamino acids medium with shaking in a air incubator Model G25 from New Brunswick Scientific (Edison, New Jersey). Growth is monitored at OD600 until it reaches a value of 1, at which time nalidixic acid (10 milligrams/mL) in 0.1 N NaOH is added to a final

concentration of 50 µg/mL. The cultures are then shaken at 37°C for three to four additional hours. A high degree of aeration is maintained throughout culture period in order to achieve maximal production of the desired gene product. The cells are examined under a light microsccpe for the presence of inclusion bodies (IB). One mL aliquots of the culture are removed for analysis of protein content by boiling the pelleted cells, treating them with reducing buffer and electrophoresis via SDS-PAGE (see Maniatis et al. Molecular Cloning: A Laboratory Manual, 1982). The culture is centrifuged (5000 x g) to pellet the cells.

Inclusion Body preparation, Extraction, Refolding, Dialysis, DEAE Chromatography, and Characterization of the G-CSF receptor agonists which accumulate as inclusion bodies in *E. coli*.

Isolation of Inclusion Bodies:

The cell pellet from a 330 mL *E. coli* culture is resuspended in 15 mL of sonication buffer (10 mM 2-amino-2-(hydroxymethyl) 1,3-propanediol hydrochloride (Tris-HCl), pH 8.0 + 1 mM ethylenediaminetetraacetic acid (EDTA)). These resuspended cells are sonicated using the microtip probe of a Sonicator Cell Disruptor (Model W-375, Heat Systems-Ultrasonics, Inc., Farmingdale, New York). Three rounds of sonication in sonication buffer followed by centrifugation are employed to disrupt the cells and wash the inclusion bodies (IB). The first round of sonication is a 3 minute burst followed by a 1 minute burst, and the final two rounds of sonication are for 1 minute each.

Extraction and refolding of proteins from inclusion body pellets:

Following the final centrifugation step, the IB pellet is resuspended in 10 mL of 50 mM Tris-HCl, pH 9.5, 8 M urea and 5 mM dithiothreitol (DTT) and stirred at room temperature for approximately 45 minutes to allow for denaturation of the expressed protein.

The extraction solution is transferred to a beaker containing 70 mL of 5mM Tris-HCl, pH 9.5 and 2.3 M urea and gently stirred while exposed to air at 4°C for 18 to 48 hours to allow the proteins to refold. Refolding is monitored by analysis on a Vydac (Hesperia, Ca.) C18 reversed phase high pressure liquid chromatography (RP-HPLC) column (0.46x25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed to monitor the refold. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Denatured proteins generally elute later in the gradient than the refolded proteins.

Purification:

Following the refold, contaminating *E. coli* proteins are removed by acid precipitation. The pH of the refold solution is titrated to between pH 5.0 and pH 5.2 using 15% (v/v) acetic acid (HOAc). This solution is stirred at 4°C for 2 hours and then centrifuged for 20 minutes at 12,000 x g to pellet any insoluble protein.

The supernatant from the acid precipitation step is dialyzed using a Spectra/Por 3 membrane with a molecular weight cut off (MWCO) of 3,500 daltons. The dialysis is against 2 changes of 4 liters (a 50-fold excess) of 10mM Tris-HCl, pH 8.0 for a total of 18 hours. Dialysis lowers the sample conductivity and removes urea prior to DEAE chromatography. The sample is then centrifuged (20 minutes at 12,000 x g) to pellet any insoluble protein following dialysis.

A Bio-Rad Bio-Scale DEAE2 column (7 x 52 mm) is used for ion exchange chromatography. The column is equilibrated in a buffer containing 10mM Tris-HCl, pH 8.0. The protein is eluted using a 0-to-500 mM sodium chloride (NaCl) gradient, in equilibration buffer, over 45 column volumes. A flow rate of 1 mL per minute is used throughout the run. Column fractions (2 mL per fraction) are collected across the gradient and analyzed by RP HPLC on a Vydac (Hesperia, Ca.) C18 column (0.46 x 25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Pooled fractions are then dialyzed against 2 changes of 4 liters (50-to-500-fold excess) of 10 mM ammonium acetate (NH_4Ac), pH 4.0 for a total of 18 hours. Dialysis is performed using a Spectra/Por 3 membrane with a MWCO of 3,500 daltons. Finally, the sample is sterile filtered using a 0.22µm syringe filter (µStar LB syringe filter, Costar, Cambridge, Ma.), and stored at 4°C.

In some cases the folded proteins can be affinity purified using affinity reagents such as mAbs or receptor subunits attached to a suitable matrix. Alternatively, (or in addition) purification can be accomplished using any of a variety of chromatographic methods such as: ion exchange, gel filtration or hydrophobic chromatography or reversed phase HPLC.

These and other protein purification methods are described in detail in Methods in Enzymology, Volume 182 'Guide to Protein Purification' edited by Murray Deutscher, Academic Press, San Diego, CA (1990).

Protein Characterization:

The purified protein is analyzed by RP-HPLC, electrospray mass spectrometry, and SDS-PAGE. The protein quantitation is done by amino acid composition, RP-HPLC, and Bradford protein determination. In some cases tryptic peptide mapping is performed in conjunction with electrospray mass spectrometry to confirm the identity of the protein.

AML Proliferation Assay

The factor-dependent cell line AML 193 was obtained from the American Type Culture Collection (ATCC, Rockville, MD). This cell line, established from a patient with acute myelogenous leukemia, is a growth factor dependent cell line which displayed enhanced growth in GM-CSF supplemented medium (Lange, B., et al., *Blood* **70**: 192, 1987; Valtieri, M., et al., *J. Immunol.* **138**:4042, 1987). The ability of AML 193 cells to proliferate in the presence of human IL-3 has also been documented. (Santoli, D., et al., *J. Immunol.* **139**: 348, 1987). A cell line variant was used, AML 193 1.3, which was adapted for long term growth in IL-3 by washing out the growth factors and starving the cytokine dependent AML 193 cells for growth factors for 24 hours. The cells are then replated at $1x10^5$ cells/well in a 24 well plate in media containing 100 U/mL IL-3. It took approximately 2 months for the cells to grow rapidly in IL-3. These cells are maintained as AML 193 1.3 thereafter by supplementing tissue culture medium (see below) with human IL-3.

AML 193 1.3 cells are washed 6 times in cold Hanks balanced salt solution (HBSS, Gibco, Grand Island, NY) by centrifuging cell suspensions at 250 x g for 10 minutes followed by decantation of the supernatant. Pelleted cells are resuspended in HBSS and the procedure is repeated until six wash cycles are completed. Cells washed six times by this procedure are resuspended in tissue culture medium at a density ranging from 2×10^5 to 5×10^5 viable cells/mL.

This medium is prepared by supplementing Iscove's modified Dulbecco's Medium (IMDM, Hazelton, Lenexa, KS) with albumin, transferrin, lipids and 2-mercaptoethanol. Bovine albumin (Boehringer-Mannheim, Indianapolis, IN) is added at 500 µg/mL; human transferrin (Boehringer-Mannheim, Indianapolis, IN) is added at 100 µg/mL; soybean lipid (Boehringer-Mannheim, Indianapolis, IN) is added at 50 µg/mL; and 2-mercaptoethanol (Sigma, St. Louis, MO) is added at 5×10^{-5} M.

Serial dilutions of G-CSF receptor agonist proteins are made in triplicate series in tissue culture medium supplemented as stated above in 96 well Costar 3596 tissue culture plates. Each well contained 50 µl of medium containing G-CSF receptor agonist proteins once serial dilutions are completed. Control wells contained tissue culture medium alone (negative control). AML 193 1.3 cell suspensions prepared as above are added to each well by pipetting 50 µl (2.5×10^4 cells) into each well. Tissue culture plates are incubated at 37°C with 5% CO_2 in humidified air for 3 days. On day 3, 0.5 µCi ^{3}H-thymidine (2 Ci/mM, New England Nuclear, Boston, MA) is added in 50 µl of tissue culture medium. Cultures are incubated at 37°C with 5% CO_2 in humidified air for 18-24 hours. Cellular DNA is harvested onto glass filter mats (Pharmacia LKB, Gaithersburg, MD) using a TOMTEC cell harvester (TOMTEC, Orange, CT) which utilized a water wash cycle followed by a 70% ethanol wash cycle. Filter mats are allowed to air dry and then placed into sample bags to which scintillation fluid (Scintiverse II, Fisher Scientific, St. Louis, MO or BetaPlate Scintillation Fluid, Pharmacia LKB, Gaithersburg, MD) is added. Beta emissions of samples from individual tissue culture wells are counted in a LKB BetaPlate model 1205 scintillation counter (Pharmacia LKB, Gaithersburg, MD) and data is expressed as counts per minute of ^{3}H-thymidine incorporated into cells from each tissue culture well.

Activity of each G-CSF receptor agonist proteins preparation is quantitated by measuring cell proliferation (^{3}H-thymidine incorporation) induced by graded concentrations of G-CSF receptor agonist. Typically, concentration ranges from 0.05 pM - 10^5 pM are quantitated in these assays. Activity is determined by measuring the dose of G-CSF receptor agonist protein which provides 50% of maximal proliferation (EC_{50} = 0.5 x (maximum average counts per minute of ^{3}H-thymidine incorporated per well among triplicate cultures of all concentrations of G-CSF receptor agonists tested - background proliferation measured by ^{3}H-thymidine incorporation observed in triplicate cultures lacking any factor). This EC_{50} value is also equivalent to 1 unit of bioactivity. Every assay is performed with native interleukin-3 and G-CSF as reference standards so that relative activity levels could be assigned.

Typically, the G-CSF receptor agonist proteins were tested in a concentration range of 2000 pM to 0.06 pM titrated in serial 2 fold dilutions.

Activity for each sample was determined by the concentration which gave 50% of the maximal response by fitting a four-parameter logistic model to the data. It was observed that the upper plateau (maximal response) for the sample and the standard with which it was compared did not differ. Therefore relative potency calculation for each sample was determined from EC50 estimations for the sample and the standard as indicated above.

Other in vitro cell based proliferation assays

Other in vitro cell based proliferation assays, known to those skilled in the art, may also be useful to determine the activity of the G-CSF receptor agonists in a similar manner as described in the AML 193.1.3 cell proliferation assay.

Transfected cell lines:

Cell lines, such as BHK or the murine pro B cell line Baf/3, can be transfected with a colony stimulating factor receptor, such as the human G-CSF receptor which the cell line does not have. These transfected cell lines can be used to determine the activity of the ligand of which the receptor has been transfected.

EXAMPLE 1

Construction of pMON3485

The new N-terminus/C-terminus gene in pMON3485 was created using Method I as described in Materials and Methods. Fragment Start was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 39 start (SEQ ID NO:7) and L-11 start (SEQ ID NO:3). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037 (WO 95/21254), using the primer set, 38 stop (SEQ ID NO:8) and L-11 stop (SEQ ID NO:4). The full-length new N terminus/C-terminus G-CSF Ser^{17} gene was created and amplified from the annealed Fragments Start and Stop using the primers 39 start (SEQ ID NO:7) and 38 stop (SEQ ID NO:8).

The resulting DNA fragment which contains the new gene was digested with restriction endonucleases NcoI and HindIII and purified using a Magic DNA Clean-up System kit (Promega, Madison, WI). The plasmid, pMON3934 (derivative of pMON3359), was digested with restriction endonucleases HindIII and NcoI, resulting in an approximately 3800 base pair vector fragment, and gel-purified. The purified restriction fragments were combined and ligated using T4 DNA ligase. A portion of the ligation reaction was used to

transform *E. coli* strain DH5α cells (Life Technologies, Gaithersburg, MD). Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3485.

BHK cells were transfected with the plasmid, pMON3485, for protein expression and bioassay.

The plasmid, pMON3485 containing the gene sequence of (SEQ ID NO:25), encodes the following amino acid sequence:

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:43)

EXAMPLE 2

Construction of pMON3486

The new N-terminus/C-terminus gene in pMON3486 was created using Method I as described in Materials and Methods. Fragment Start was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037, using the primer set, 97 start (SEQ ID NO:9) and L-11 start (SEQ ID NO:3). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 96 stop

(SEQ ID NO:10) and L-11 stop (SEQ ID NO:4). The full-length new N terminus/C-terminus G-CSF Ser^{17} gene was created and amplified from the annealed Fragments Start and Stop using the primers 97 start (SEQ ID NO:9) and 96 stop (SEQ ID NO:10).

The resulting DNA fragment which contains the new gene was digested with restriction endonucleases NcoI and HindIII and gel-purified using a Magic DNA Clean-up System kit. The plasmid, pMON3934, was digested with restriction endonucleases HindIII and NcoI, resulting in an approximately 3800 base pair vector fragment, and gel-purified. The purified restriction fragments were combined and ligated using T4 DNA ligase. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3486.

BHK cells were transfected with the plasmid, pMON3486, for protein expression and bioassay.

The plasmid, pMON3486 containing the gene sequence of (SEQ ID NO:26), encodes the following amino acid sequence:

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:44)

EXAMPLE 3

Construction of pMON3487

The new N-terminus/C-terminus gene in pMON3487 was created using Method I as described in Materials and Methods. Fragment Start was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037, using the primer set, 126 start (SEQ ID NO:11) and L-11 start (SEQ ID NO:3). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 125 stop (SEQ ID NO:12) and L-11 stop (SEQ ID NO:4). The full-length new N terminus/C-terminus G-CSF Ser^{17} gene was created and amplified from the annealed Fragments Start and Stop using the primers 126 start (SEQ ID NO:11) and 125 stop (SEQ ID NO:12).

The resulting DNA fragment which contains the new gene was digested with restriction endonucleases NcoI and HindIII and purified using a Magic DNA Clean-up System kit. The plasmid, pMON3934, was digested with restriction endonucleases HindIII and NcoI, resulting in an approximately 3800 base pair vector fragment, and gel-purified. The purified restriction fragments were combined and ligated using T4 DNA ligase. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3487.

BHK cells were transfected with the plasmid, pMON3487, for protein expression and bioassay.

The plasmid, pMON3487 containing the gene sequence of (SEQ ID NO:27), encodes the following amino acid sequence:

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro
Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala
Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys
Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu
Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp
Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
Gln Met Glu Glu Leu Gly (SEQ ID NO:45)

EXAMPLE 4

Construction of pMON3488

The new N-terminus/C-terminus gene in pMON3488 was created using Method I as described in Materials and Methods. Fragment Start was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037, using the primer set, 133 start (SEQ ID NO:13) and L-11 start (SEQ ID NO:3). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037 using the primer set, 132 stop (SEQ ID NO:14) and L-11 stop (SEQ ID NO:4). The full-length new N terminus/C-terminus G-CSF Ser^{17} gene was created and amplified from the annealed Fragments Start and Stop using the primers 133 start (SEQ ID NO:13) and 132 stop (SEQ ID NO:14).

The resulting DNA fragment which contains the new gene was dig sted with restriction endonucleases NcoI and HindIII and purified using a Magic DNA Clean-up System kit. The

plasmid, pMON3934, was digested with restriction endonucleases HindIII and NcoI, resulting in an approximately 3800 base pair vector fragment, and gel-purified. The purified restriction fragments were combined and ligated using T4 DNA ligase. A portion of the ligation reaction was used to transform *E. coli* strain DH5αcells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3488.

BHK cells were transfected with the plasmid, pMON3488, for protein expression and bioassay.

The plasmid, pMON3488 containing the gene sequence of (SEQ ID NO:28), encodes the following amino acid sequence:

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly
Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys
Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly
His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro (SEQ ID NO:46)

EXAMPLE 5

Construction of pMON3489

The new N-terminus/C-terminus gene in pMON3489 was created using Method I as described in Materials and

Methods. Fragment Start was created and amplified from G-CSF Ser^{17} sequence in the plasmid, pMON13037, using the primer set, 142 start (SEQ ID NO:15) and L-11 start (SEQ ID NO:3). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 141 stop (SEQ ID NO:16) and L-11 stop (SEQ ID NO:4). The full-length new N terminus/C-terminus G-CSF Ser^{17} gene was created and amplified from the annealed Fragments Start and Stop using the primers 142 start (SEQ ID NO:15) and 141 stop (SEQ ID NO:16).

The resulting DNA fragment which contains the new gene was digested with restriction endonucleases NcoI and HindIII and purified using a Magic DNA Clean-up System kit. The plasmid, pMON3934, was digested with restriction endonucleases HindIII and NcoI, resulting in an approximately 3800 base pair vector fragment, and gel-purified. The purified restriction fragments were combined and ligated using T4 DNA ligase. A portion of the ligation reaction was used to transform *E. coli* strain DH5αcells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3489.

BHK cells were transfected with the plasmid, pMON3489, for protein expression and bioassay.

The plasmid, pMON3489 containing the gene sequence of (SEQ ID NO:29), encodes the following amino acid sequence:

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu
Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
Ala Met Pro Ala Phe Ala (SEQ ID NO:47)

EXAMPLE 6

Construction of pMON3490

The new N-terminus/C-terminus gene in pMON3490 was created using Method II as described in Materials and Methods. Fragment Start was created and amplified from G-CSF sequence in the plasmid, pMON13037, using the primer set, 39 start (SEQ ID NO:7) and P-bl start (SEQ ID NO:5). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 38 stop (SEQ ID NO:8) and P-bl stop (SEQ ID NO:6). Fragment Start was digested with restriction endonuclease NcoI, and Fragment Stop was digested with restriction endonuclease HindIII. After purification, the digested Fragments Start and Stop were combined with and ligated to the approximately 3800 base pair NcoI-HindIII vector fragment of pMON3934. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3490.

BHK cells were transfected with the plasmid, pMON3490, for protein expression and bioassay.

The plasmid, pMON3490 containing the gene sequence of (SEQ ID NO:30), encodes the following amino acid sequence:

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala
Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe
Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln
Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:48)

EXAMPLE 7

Construction of pMON3491

The new N-terminus/C-terminus gene in pMON3491 was created using Method II as described in Materials and Methods. Fragment Start was created and amplified from G-CSF sequence in the plasmid, pMON13037, using the primer set, 97 start (SEQ ID NO:9) and P-bl start (SEQ ID NO:5). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 96 stop (SEQ ID NO:10) and P-bl stop (SEQ ID NO:6). Fragment Start was digested with restriction endonuclease NcoI, and Fragment Stop was digested with restriction endonuclease HindIII. After purification, the digested Fragments Start and Stop were combined with and ligated to the approximately 3800 base pair NcoI-HindIII vector fragment of pMON3934. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3491.

BHK cells were transfected with the plasmid, pMON3491, for protein expression and bioassay.

The plasmid, pMON3491 containing the gene sequence of (SEQ ID NO:31), encodes the following amino acid sequence:

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:49)

EXAMPLE 8

Construction of pMON3492

The new N-terminus/C-terminus gene in pMON3492 was created using Method II as described in Materials and Methods. Fragment Start was created and amplified from G-CSF sequence in the plasmid, pMON13037, using the primer set, 126 start (SEQ ID NO:11) and P-bl start (SEQ ID NO:5). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 125 stop (SEQ ID NO:12) and P-bl stop (SEQ ID NO:6). Fragment Start was digested with restriction endonuclease NcoI, and Fragment Stop was digested with restriction endonuclease HindIII. After purification, the digested Fragments Start and Stop were combined with and ligated to the approximately 3800

base pair NcoI-HindIII vector fragment of pMON3934. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3492.

BHK cells were transfected with the plasmid, pMON3492, for protein expression and bioassay.

The plasmid, pMON3492 containing the gene sequence of (SEQ ID NO:32), encodes the following amino acid sequence:

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:50)

EXAMPLE 9

Construction of pMON3493

The new N-terminus/C-terminus gene in pMON3493 was created using Method II as described in Materials and Methods. Fragment Start was created and amplified from G-CSF sequence in the plasmid, pMON13037, using the primer set, 133 start (SEQ ID NO:13) and P-bl start (SEQ ID NO:5).

Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 132 stop (SEQ ID NO:14) and P-bl stop (SEQ ID NO:6). Fragment Start was digested with restriction endonuclease NcoI, and Fragment Stop was digested with restriction endonuclease HindIII. After purification, the digested Fragments Start and Stop were combined with and ligated to the approximately 3800 base pair NcoI-HindIII vector fragment of pMON3934. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3493.

BHK cells were transfected with the plasmid, pMON3493, for protein expression and bioassay.

The plasmid, pMON3493 containing the gene sequence of (SEQ ID NO:33), encodes the following amino acid sequence:

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu
Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:51)

EXAMPLE 10

Construction of pMON3494

The new N-terminus/C-terminus gene in pMON3494 was created using Method II as described in Materials and Methods. Fragment Start was created and amplified from G-CSF sequence in the plasmid, pMON13037, using the primer set, 142 start (SEQ ID NO:15) and P-bl start (SEQ ID NO:5). Fragment Stop was created and amplified from G-CSF Ser^{17} sequence in pMON13037 using the primer set, 141 stop (SEQ ID NO:16) and P-bl stop (SEQ ID NO:6). Fragment Start was digested with restriction endonuclease NcoI, and Fragment Stop was digested with restriction endonuclease HindIII. After purification, the digested Fragments Start and Stop were combined with and ligated to the approximately 3800 base pair NcoI-HindIII vector fragment of pMON3934. A portion of the ligation reaction was used to transform *E. coli* strain DH5α cells. Transformant bacteria were selected on ampicillin-containing plates. Plasmid DNA was isolated and sequenced to confirm the correct insert. The resulting plasmid was designated pMON3494.

BHK cells were transfected with the plasmid, pMON3494, for protein expression and bioassay.

The plasmid, pMON3494 containing the gene sequence of (SEQ ID NO:34), encodes the following amino acid sequence:

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile

Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:52)

Examples 11-20

The genes encoding the G-CSF receptor agonists of Examples 1-10 were excised from the BHK vectors as a NcoI/HindIII fragment and ligated with the ~ 3630 base pair NcoI/HindIII vector fragment of pMON2341 (WO 94/12638). The resulting plasmids (Examples 11-20) are indicated in Table 4. The plasmids were transformed into *E. coli* strain JM101 cells and expression of the G-CSF receptor agonist protein was evaluated. The proteins expressed are the same as those expressed in the parental BHK expression vector except the proteins were immediately preceded by a Methionine-Alanine dipeptide and the Methionine is processed off by methionine aminopeptidase. Overnight growths of cells (20 Klett units) were inoculated in 10mL of minimal M9 medium supplemented with vitamin B1 and trace minerals and incubated with shaking at 37°C until initial Klett readings of ~120 units were obtained. At 120 Klett units 50uL of 10mg/mL nalidixic acid was added. Four hours post-induction, a 1ml aliquot was removed for protein expression analysis by SDS-PAGE. Cells were also examined using light microscopy for the presence of inclusion bodies. Only pMON3450 and pMON3455 had significant expression levels of the G-CSF receptor agonist protein. In an effort to improve expression levels of G-CSF receptor agonists, the 5' end of the genes were re-engineered to incorporate AT-rich codons and *E. coli* preferred codons between the unique NcoI and NheI restriction endonuclease recognition sites (Examples 21-28).

TABLE 4
E. coli expression plasmids

Example #	Resulting *E. coli* expression plasmid pMON#	Breakpoint	Linker	Parental BHK plasmid pMON#
Example 11	pMON3450	38/39	zero	pMON3490
Example 12	pMON3455	38/39	Δ1-10	pMON3485
Example 13	pMON3451	96/97	zero	pMON3491
Example 14	pMON3456	96/97	Δ1-10	pMON3486
Example 15	pMON3452	125/126	zero	pMON3492
Example 16	pMON3457	125/126	Δ1-10	pMON3487
Example 17	pMON3453	132/133	zero	pMON3493
Example 18	pMON3458	132/133	Δ1-10	pMON3488
Example 19	pMON3454	141/142	zero	pMON3494
Example 20	pMON3459	141/142	Δ1-10	pMON3489

Example 21

Construction of pMON25184

The complementary pair of synthetic oligomers, 141for.seq (SEQ ID NO:23) and 141rev.seq (SEQ ID NO:24), (Midland Certified Reagent Co., Midland TX) were annealed by heating 2ug of each synthetic oligomer in a 20ul reaction mixture containing 20mM Tris-HCl (7.5), 10mM $MgCl_2$, and 50mM NaCl, at 80°C for 5 minutes, and allowing the mixture to slowly cool to ambient temperature (approximately 45 minutes). When properly annealed the oligomers create an NcoI site at the 5′ end and a NheI site at the 3′ end. Approximately 15 ng of the annealed oligomer pair was ligated with the gel-purified ~ 4120 base pair NcoI/NheI

vector fragment of pMON3454 (~molar ratio of 10:1). The resulting gene, had seven codon changes at the 5' end of the gene. The ligation reaction was used to transform *E. coli* strain DH5α and the desired codon changes were confirmed by DNA sequence analysis. The resulting plasmid was designated pMON25184. Plasmid, pMON25184 containing the gene sequence of (SEQ ID NO:38), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3454.

Example 22

Construction of pMON25188

The complementary pair of synthetic oligomers, 141for.seq (SEQ ID NO:23) and 141rev.seq (SEQ ID NO:24), (Midland Certified Reagent Co., Midland TX) were annealed by heating 2ug of each synthetic oligomer in a 20ul reaction mixture containing 20mM Tris-HCl (7.5), 10mM $MgCl_2$, and 50mM NaCl, at 80°C for 5 minutes, and allowing the mixture to slowly cool to ambient temperature (approximately 45 minutes). When properly annealed the oligomers create an NcoI site at the 5' end and a NheI site at the 3' end. Approximately 15ng of the annealed oligomer pair was ligated with the ~ 4110 base pair NcoI/NheI gel-purified pMON3459 (~molar ratio of 10:1). The ligation mixture was used to transform *E. coli* strain DH5α and the desired codon changes were confirmed by DNA sequence analysis. The resulting plasmid was designated pMON25188. The resulting gene, had seven codon changes at the 5' end of the gene. Plasmid, pMON25188 containing the gene sequence of (SEQ ID NO:42), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3459.

Example 23

Construction of pMON25183

pMON25183 was constructed using an overlapping PCR primer method. The synthetic oligomers, 132for.seq (SEQ ID NO:321 and 132rev.seq (SEQ ID NO:22), encode the NcoI and NheI restriction recognition sequence, respectively. Amplified DNA was generated by the DNA polymerase chain amplification method using the PCR Optimizer Kit (Invitrogen). The PCR reactions were performed using the manufacturer's recommended conditions using 5X buffer B (300mM Tris-HCl pH8.5, 75 mM $(NH_4)_2SO_4$, 10mM $MgCl_2$) for seven cycles consisting of 94°C for 1', 65°C for 2', and 72°C for 2', followed by 20 cycles of 94°C for 1', and 72°C for 3', and a final cycle of 7 minutes at 72°C using a Perkin Elmer Model 480 DNA thermal cycler (Perkin Elmer). The reaction product was desalted using Centri-Sep spin columns (Princeton Separations) following the manufacturer's recommended protocol, digested with NcoI/NheI, and gel purified from TAE-agarose gels using Gene Clean (Bio 101) and the DNA product was eluted in dH_2O The purified PCR product was ligated with the ~ 4090 base pair NcoI/NheI pMON3453 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting plasmid was designated pMON25183. The resulting gene, had 14 codon changes at the 5' end of the gene. Plasmid, pMON25183 containing the gene sequence of (SEQ ID NO:37), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3453.

Example 24

Construction of pMON25187

pMON25187 was constructed using an overlapping PCR primer method. The synthetic oligomers, 132for.seq (SEQ ID NO:21) and 132rev.seq (SEQ ID NO:22), encode the NcoI and NheI restriction recognition sequence, respectively. Amplified DNA was generated by the DNA polymerase chain amplification method using the PCR Optimizer Kit (Invitrogen). The PCR reactions were performed using the manufacturer's recommended conditions, in 5X buffer B for seven cycles consisting of 94°C for 1', 65°C for 2', and 72°C for 2', followed by 20 cycles of 94°C for 1', and 72°C for 3', and a final cycle of 7 minutes at 72°C using a Perkin Elmer Model 480 DNA thermal cycler (Perkin Elmer). The reaction product was desalted using Centri-Sep spin columns (Princeton Separations) following the manufacturer's recommended protocol, digested with NcoI/NheI, and gel purified from TAE-agarose gels using Gene Clean (Bio 101) and the DNA product was eluted in dH_2O. The purified PCR product was ligated with the ~ 4080 base pair NcoI/NheI pMON3458 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting plasmid was designated pMON25187. The resulting gene, had 14 codon changes at the 5' end of the gene. Plasmid, pMON25187 containing the gene sequence of (SEQ ID NO:41), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3458.

Example 25

Construction of pMON25182

pMON25182 was constructed using the overlapping PCR primer approach described in Example 23. The synthetic oligomer primers 125for.seq (SEQ ID NO:19) and 125rev.seq

(SEQ ID NO:20) were used in the PCR reaction. The PCR reaction conditions were identical to those used in Example 23 except the annealing temperature for the first seven cycles was 60°C. The purified PCR product was ligated with ~ 4070 base pair NcoI/NheI pMON3452 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting plasmid was designated pMON25182. The resulting gene, had 19 codon changes at the 5' end of the gene. Plasmid, pMON25182 containing the gene sequence of (SEQ ID NO:36), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3452.

Example 26

Construction of pMON25186

pMON25186 was constructed using the overlapping PCR primer approach described in Example 23. The synthetic oligomer primers 125for.seq (SEQ ID NO:19) and 125rev.seq (SEQ ID NO:20) were used in the PCR reaction. The PCR reaction conditions were identical to those used in Example 23 except the annealing temperature for the first seven cycles was 60°C. The purified PCR product was ligated with the ~ 4060 base pair NcoI/NheI pMON3457 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting plasmid was designated pMON25186. The resulting gene, had 19 codon changes at the 5' end of the gene. Plasmid, pMON25186 containing the gene sequence of (SEQ ID NO:40), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3457.

Examples 27

Construction of pMON25181

pMON25181 was constructed using PCR to amplify a DNA fragment from pMON3451 as the template using the oligomers 96for.seq (SEQ ID NO:17) and 96rev.seq (SEQ ID NO:18). The oligomer 96for.seq was designed to create six codon changes. The PCR reaction conditions were the same as described in Example 25, except 10ng of pMON3451 plasmid DNA was added. The purified PCR product was ligated with the ~ 3980 base pair NcoI/NheI pMON3451 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting plasmid was designated pMON25181. The resulting gene, had 6 codon changes at the 5' end of the gene. Plasmid, pMON25181 containing the gene sequence of (SEQ ID NO:35), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3451.

Examples 28

Construction of pMON25185

pMON25185 was constructed using PCR to amplify a DNA fragment from pMON3451 as the template using the oligomers 96for.seq (SEQ ID NO:17) and 96rev.seq (SEQ ID NO:18). The oligomer 9697for.seq was designed to create six codon changes. The PCR reaction conditions were the same as described in Example 25, except 10ng of pMON3456 plasmid DNA was added. The purified PCR product was ligated with the ~ 3970 base pair NcoI/NheI pMON3456 vector fragment. Positive clones containing the AT-rich replacement insert were identified as described in Example 21. The resulting

plasmid was designated pMON25185. The resulting gene, had 6 codon changes at the 5' end of the gene. Plasmid, pMON25185 containing the gene sequence of (SEQ ID NO:39), DNA was retransformed into *E. coli* strain JM101 cells for protein expression. The protein expressed is the same as that expressed from pMON3456.

EXAMPLE 29

The G-CSF amino acid substitution variants of the present invention were made using PCR mutagenesis techniques as described in WO 94/12639 and WO 94/12638. These and other variants (i.e. amino acid substitutions, insertions or deletions and N-terminal or C-terminal extensions) could also be made, by one skilled in the art, using a variety of other methods including synthetic gene assembly or site-directed mutagenesis (see Taylor et al., *Nucl. Acids Res.*, **13**:7864-8785, 1985; Kunkel et al., *Proc. Natl. Acad. Sci. USA*, **82**:488-492, 1985; Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, WO 94/12639 and WO 94/12638). These substitutions can be made one at a time or in combination with other amino acid substitutions, and/or deletions, and/or insertions and/or extensions. After sequence verification of the changes, the plasmid DNA can be transfected into an appropriate mammalian cell, insect cell or bacterial strain such as *E. coli* for production. Known variants of G-CSF, which are active, include substitutions at positions 1 (Thr to Ser, Arg or Gly, 2 (Pro to Leu), 3 (Leu to Arg or Ser) and 17 (Cys to Ser) and deletions of amino acids 1-11 (Kuga et al. *Biochemicla and Biophysical Research Comm.* **159**:103-111, 1989). It is understood that these G-CSF amino acid substitution variants could serve as the template sequence for the rearrangement of the amino acid sequence as described in the other examples.

Bioactivity determination of G-CSF amino acid substitution variants.

The G-CSF amino acid substitution variants were assayed in the Baf/3 cell line, transfected with the human G-CSF receptor, proliferation assay to determine their bioactivity relative to native G-CSF. The G-CSF variants tested and their relative bioactivity are shown in Table 5. A "+" indicates that the activity was comparable to native G-CSF and "-" indicates that the activity was significantly decreased or not detected.

TABLE 5

CELL PROLIFERATION ACTIVITY OF G-CSF VARIANTS IN BAF/3 CELL LINE TRANSFECTED WITH THE HUMAN G-CSF RECEPTOR

aa position	native aa	mutant aa	activity *
13	Phe	Ser	+
13	Phe	His	+
13	Phe	Thr	+
13	Phe	Pro	+
16	Lys	Pro	+
16	Lys	Ser	+
16	Lys	Thr	+
16	Lys	His	+
18	Leu	Pro	+
18	Leu	Thr	+
18	Leu	His	+
18	Leu	Cys	+
18	Leu	Ile	+
19	Glu	Ala	-
19	Glu	Thr	-
19	Glu	Arg	-
19	Glu	Pro	-
19	Glu	Leu	-
19	Glu	Gly	-
19	Glu	Ser	-
22	Arg	Tyr	+
22	Arg	Ser	+
22	Arg	Ala	+
22	Arg	Val	+
22	Arg	Thr	+
24	Ile	Pro	+
24	Ile	Leu	+
24	Ile	Tyr	+

TABLE 5 cont.

aa position	native aa	mutant aa	activity *
27	Asp	Gly	+
30	Ala	Ile	+
30	Ala	Leu	+
34	Lys	Ser	+
43	His	Gly	+
43	His	Thr	+
43	His	Val	+
43	His	Lys	+
43	His	Trp	+
43	His	Ala	+
43	His	Arg	+
43	His	Cys	+
43	His	Leu	+
44	Pro	Arg	+
44	Pro	Asp	+
44	Pro	Val	+
44	Pro	Ala	+
44	Pro	His	+
44	Pro	Gln	+
44	Pro	Trp	+
44	Pro	Gly	+
44	Pro	Thr	+
46	Glu	Ala	+
46	Glu	Arg	+
46	Glu	Phe	+
46	Glu	Ile	+
47	Leu	Thr	+
49	Leu	Phe	+
49	Leu	Arg	+
49	Leu	Ser	+

TABLE 5 cont.

aa position	native aa	mutant aa	activity *
50	Leu	His	+
50	Leu	Pro	+
51	Gly	Ser	+
51	Gly	Met	+
54	Leu	His	+
67	Gln	Lys	+
67	Gln	Leu	+
67	Gln	Cys	+
67	Gln	Lys	+
70	Gln	Pro	+
70	Gln	Leu	+
70	Gln	Arg	+
70	Gln	Ser	+
104	Asp	Gly	+
104	Asp	Val	+
108	Leu	Ala	+
108	Leu	Val	+
108	Leu	Arg	+
108	Leu	Gly	+
108	Leu	Trp	+
108	Leu	Gln	+
115	Thr	His	+
115	Thr	Leu	+
115	Thr	Ala	+
115	Thr	Ile	+
120	Gln	Gly	+
120	Gln	Arg	+
120	Gln	Lys	+
120	Gln	His	+

TABLE 5 cont.

aa position	native aa	mutant aa	activity *
123	Glu	Arg	+
123	Glu	Phe	+
123	Glu	Thr	+
144	Phe	His	+
144	Phe	Arg	+
144	Phe	Pro	+
144	Phe	Leu	+
144	Phe	Glu	+
146	Arg	Gln	+
147	Arg	Gln	+
156	His	Asp	-
156	His	Ser	+
156	His	Gly	+
159	Ser	Arg	+
159	Ser	Thr	+
159	Ser	Tyr	+
159	Ser	Val	+
159	Ser	Gly	+
162	Glu	Gly	-
162	Glu	Trp	+
162	Glu	Leu	+
163	Val	Arg	+
163	Val	Ala	+
163	Val	Gly	+
165	Tyr	Cys	not determined
169	Ser	Leu	+
169	Ser	Cys	+
169	Ser	Arg	+
170	His	Arg	+
170	His	Ser	+

EXAMLPLE 30-37

Examples 30-37 were made in a similar manner as described in Example 6 using the plasmid pMON13037 as the template and the oligonucleotide primers indicated in Table 6. The resulting gene and the designated plasmid pMON # and the protein encoded are indicated in Table 6.

TABLE 6

Example	breakpoint	primers	resulting gene	resulting protein
30	48/49	49start (SEQ ID NO:68) 48stop (SEQ ID NO:69)	pMON3460 (SEQ ID NO:86)	(SEQ ID NO:95)
31	76/77	77start (SEQ ID NO:70) 76stop (SEQ ID NO:71)	pMON3461 (SEQ ID NO:87)	(SEQ ID NO:96)
32	81/82	82start (SEQ ID NO:72) 81stop (SEQ ID NO:73)	pMON3462 (SEQ ID NO:88)	(SEQ ID NO:97)
33	83/84	84start (SEQ ID NO:74) 83stop (SEQ ID NO:75)	pMON3463 (SEQ ID NO:88)	(SEQ ID NO:98)
34	90/91	91start (SEQ ID NO:76) 90stop (SEQ ID NO:77)	pMON3464 (SEQ ID NO:89)	(SEQ ID NO:99)
35	111/112	112start (SEQ ID NO:78) 111stop (SEQ ID NO:79)	pMON3465 (SEQ ID NO:90)	(SEQ ID NO:100)
36	116/117	117start (SEQ ID NO:80) 116stop (SEQ ID NO:81)	pMON3466 (SEQ ID NO:91)	(SEQ ID NO:101)
37	118/119	119start (SEQ ID NO:82) 118stop (SEQ ID NO:83)	pMON3467 (SEQ ID NO:92)	(SEQ ID NO:102)

The G-CSF receptor agonist genes in pMON3640, pMON3461, pMON3462, pMON3463, pMON3464, pMON3465, pMON3466 and pMON3467 were transferred to an E. coli expression vector, pMON2341, as an NcoI/HindIII restriction fragment, resulting

in the plasmids pMON3468, pMON3469, pMON3470, pMON3471, pMON3472, pMON3473, pMON3474 and pMON3498 respectively.

EXAMPLE 38

The plasmid, pMON3468, resulted in low expression levels in E. coli of the desired G-CSF receptor agonist. The 5' end of the gene was redesigned to use codon selection that was AT rich to increase expression levels. The oligonucleotides, Z4849AT.for (SEQ ID NO:84) and Z4849AT.rev (SEQ ID NO:85), were used to re-engineer the gene. The resulting plasmid, pMON3499, containing the gene (SEQ ID NO:94) encodes the G-CSF receptor agonist of (SEQ ID NO:103).

EXAMPLE 39

The G-CSF receptor agonists were assayed in the Baf/3 cell line, transfected with the human G-CSF receptor, (Baf/3-G-CSF) proliferation assay to determine their bioactivity relative to native G-CSF. The activity of the receptor agonists is shown in Table 7.

TABLE 7

G-CSF receptor agonist activity in Baf/3-G-CSF cell proliferation assay

pMON#	breakpoint	Expression	E. coli refold	EC50 (pM)
native G-CSF				60 pM
pMON25182	125/126	+	+	38 pM
pMON25183	132/133	+	+	58 pM
pMON25184	141/142	+	+	70 pM
pMON25186	125/126	+	+	92 pM
pMON25187	132/133	+	+	83 pM
pMON25188	141/142	+	+	41 pM
pMON3450	38/39	+	+	121 pM
pMON3455	38/39	+	+	102 pM
pMON3499	48/49	+	+	137 pM
pMON3470	81/82	+	+	no activity detected
pMON3473	111/112	+	-	

Additional techniques for the construction of the variant genes, recombinant protein expression , protein purification, protein characterization, biological activity determination can be found in WO 94/12639, WO 94/12638, WO 95/20976, WO 95/21197, WO 95/20977, WO 95/21254 which are hereby incorporated by reference in their entirety.

All references, patents or applications cited herein are incorporated by reference in their entirety as if written herein.

Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: G. D. Searle & Co.
(B) STREET: P. O. Box 5110
(C) CITY: Chicago
(D) STATE: Illinois
(E) COUNTRY: United States of America
(F) POSTAL CODE (ZIP): 60680
(G) TELEPHONE: (708)470-6501
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(A) NAME: Monsanto Company
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(E) COUNTRY: United States of America
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(G) TELEPHONE: (314)647-3131
(H) TELEFAX: (314)694-5435

(ii) TITLE OF INVENTION: G-CSF Receptor Agonists

(iii) NUMBER OF SEQUENCES: 103

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(v) CURRENT APPLICATION DATA:
APPLICATION NUMBER: US 2907
(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 60/004,382
(B) FILING DATE: 05-OCT-1995

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Modified-site

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      (B) LOCATION:1
      (D) OTHER INFORMATION:/note= "Xaa at position 1 is Thr,
          Ser, Arg, Tyr or Gly;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:2
      (D) OTHER INFORMATION:/note= "Xaa at position 2 is Pro or
          Leu;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:3
      (D) OTHER INFORMATION:/note= "Xaa at position 3 is Leu,
          Arg, Tyr or Ser;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:13
      (D) OTHER INFORMATION:/note= "Xaa at position 13 is Phe,
          Ser, His, Thr or Pro;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:16
      (D) OTHER INFORMATION:/note= "Xaa at position 16 is Lys,
          Pro, Ser, thr or His;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:17
      (D) OTHER INFORMATION:/note= "Xaa at position 17 is Cys,
          Ser, Gly, Ala, Ile, Tyr or Arg;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:18
      (D) OTHER INFORMATION:/note= "Xaa at position 18 is Leu,
          Thr, Pro, His, Ile or Cys;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:22
      (D) OTHER INFORMATION:/note= "Xaa at position 22 is Arg,
          Tyr, Ser, Thr or Ala;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION:24
      (D) OTHER INFORMATION:/n te= "Xaa at position 24 is Ile,
          Pro, Tyr or Leu;"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

(B) LOCATION:27
(D) OTHER INFORMATION:/note= "Xaa at position 27 is Asp, or Gly;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:30
(D) OTHER INFORMATION:/note= "Xaa at position 30 is Ala, Ile, Leu or Gly;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:34
(D) OTHER INFORMATION:/note= "Xaa at position 34 is Lys or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:36
(D) OTHER INFORMATION:/note= "Xaa at position 36 is Cys or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:42
(D) OTHER INFORMATION:/note= "Xaa at position 42 is Cys or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:43
(D) OTHER INFORMATION:/note= "Xaa at position 43 is His, Thr, Gly, Val, Lys, Trp, Ala, Arg, Cys, or Leu;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:44
(D) OTHER INFORMATION:/note= "Xaa at position 44 is Pro, Gly, Arg, Asp, Val, Ala, His, Trp, Gln, or Thr;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:46
(D) OTHER INFORMATION:/note= "Xaa at position 46 is Glu, Arg, Phe, Arg, Ile or Ala;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:47
(D) OTHER INFORMATION:/note= "Xaa at position 47 is Leu or Thr;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION:49
(D) OTHER INFORMATION:/note= "Xaa at position 49 is Leu, Phe, Arg or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:50
(D) OTHER INFORMATION:/note= "Xaa at position 50 is Leu, Ile, His, Pro or Tyr;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:54
(D) OTHER INFORMATION:/note= "Xaa at position 54 is Leu or His;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:64
(D) OTHER INFORMATION:/note= "Xaa at position 64 is Cys or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:67
(D) OTHER INFORMATION:/note= "Xaa at position 67 is Gln, Lys, Leu or Cys;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:70
(D) OTHER INFORMATION:/note= "Xaa at position 70 is Gln, Pro, Leu, Arg or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:74
(D) OTHER INFORMATION:/note= "Xaa at position 74 is Cys or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:104
(D) OTHER INFORMATION:/note= "Xaa at position 104 is Asp, Gly or Val;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:108
(D) OTHER INFORMATION:/n te= "Xaa at position 108 is Leu, Ala, Val, Arg, Trp, Gln r Gly;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION:115
(D) OTHER INFORMATION:/note= "Xaa at position 115 is Thr, His, Leu or Ala;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:120
(D) OTHER INFORMATION:/note= "Xaa at position 120 is Gln, Gly, Arg, Lys or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:123
(D) OTHER INFORMATION:/note= "Xaa at position 123 is Glu, Arg, Phe or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:144
(D) OTHER INFORMATION:/note= "Xaa at position 144 is Phe, His, Arg, Pro, Leu, Gln or Glu;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:146
(D) OTHER INFORMATION:/note= "Xaa at position146 is Arg or Gln;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:147
(D) OTHER INFORMATION:/note= "Xaa ap position 147 is Arg or Gln;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:156
(D) OTHER INFORMATION:/note= "Xaa at position 156 is His, Gly or Ser;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:159
(D) OTHER INFORMATION:/note= "Xaa at position 159 is Ser, Arg, Thr, Tyr, Val or Gly;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:162
(D) OTHER INFORMATION:/n te= "Xaa at position 162 is Glu, Leu, Gly or Trp;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION:163
(D) OTHER INFORMATION:/note= "Xaa at position 163 is Val, Gly, Arg or Ala;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:169
(D) OTHER INFORMATION:/note= "Xaa at position 169 is Arg, Ser, Leu, Arg or Cys;"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:170
(D) OTHER INFORMATION:/note= "Xaa at position 170 is His, Arg or Ser;"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Xaa Xaa Xaa Gly Pro Ala Ser Ser Leu Pro Gln Ser Xaa Leu Leu Xaa
1               5                  10                  15

Xaa Xaa Glu Gln Val Xaa Lys Xaa Gln Gly Xaa Gly Ala Xaa Leu Gln
            20                  25                  30

Glu Xaa Leu Xaa Ala Thr Tyr Lys Leu Xaa Xaa Xaa Glu Xaa Xaa Val
        35                  40                  45

Xaa Xaa Gly His Ser Xaa Gly Ile Pro Trp Ala Pro Leu Ser Ser Xaa
    50                  55                  60

Pro Ser Xaa Ala Leu Xaa Leu Ala Gly Xaa Leu Ser Gln Leu His Ser
65                  70                  75                  80

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
                85                  90                  95

Pro Glu Leu Gly Pro Thr Leu Xaa Thr Leu Gln Xaa Asp Val Ala Asp
            100                 105                 110

Phe Ala Xaa Thr Ile Trp Gln Gln Met Glu Xaa Xaa Gly Met Ala Pro
        115                 120                 125

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Xaa
    130                 135                 140

Gln Xaa Xaa Ala Gly Gly Val Leu Val Ala Ser Xaa Leu Gln Xaa Phe
145                 150                 155                 160

Leu Xaa Xaa Ser Tyr Arg Val Leu Xaa Xaa Leu Ala Gln Pr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Gly Gly Gly Ser
1

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GCTCTGAGAG CCGCCAGAGC CGCCAGAGGG CTGCGCAAGG TGGCGTAGAA CGCG
54

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

CAGCCCTCTG GCGGCTCTGG CGGCTCTCAG AGCTTCCTGC TCAAGTCTTT AGAG
54

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GGGCTGCGCA AGGTGGCG
18

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

ACACCATTGG GCCCTGCCAG C
21

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GATCGACCAT GGCTTACAAG CTGTGCCACC CC
32

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

CGATCGAAGC TTATTAGGTG GCACACAGCT TCTCCT
36

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GATCGACCAT GGCTCCCGAG TTGGGTCCCA CC
32

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CGATCGAAGC TTATTAGGAT ATCCCTTCCA GGGCCT
36

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GATCGACCAT GGCTATGGCC CCTGCCCTGC AG
32

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CGATCGAAGC TTATTATCCC AGTTCTTCCA TCTGCT
36

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: ther nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GATCGACCAT GGCTACCCAG GGTGCCATGC CG
32

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

CGATCGAAGC TTATTAGGGC TGCAGGGCAG GGGCCA
36

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GATCGACCAT GGCTTCTGCT TTCCAGCGCC GG
32

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CGATCGAAGC TTATTAGGCG AAGGCCGGCA TGGCAC
36

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

ATATCCATGG CTCCGGAACT GGGTCCAACT CTG
33

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

ACCTCCAGGA AGCTCTGCAG ATGG
24

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

TATATCCATG GCTATGGCTC CAGCTCTGCA ACCAACTCAA GGTGCAATGC CAGCATTTGC
60

ATCTG
65

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

GATGGCTAGC AACCAGAACA CCACCTGCAC GACGTTGAAA AGCAGATGCA AATGCTGGCA
60

TTG
63

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

TATATCCATG GCTACTCAAG GTGCTATGCC AGCTTTTGCT TCTGCTTTTC AACGTCG
57

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GCAGATGGCT AGCAACCAGA ACACCACCTG CACGACGTTG AAAAGCAGAA GCAAAAGC
58

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

CATGGCTTCT GCTTTTCAAC GTCGTGCAGG TGGTGTTCTG GTTG
44

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: ther nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

CTAGCAACCA GAACACCACC TGCACGACGT TGAAAAGCAG AAGC
44

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

ATGGCTTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
60

CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC
120

CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
180

CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC
240

ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
300

ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT
360

CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC ACCTTGCGCA GCCCTCTGGC
420

GGCTCTGGCG GCTCTCAGAG CTTCCTGCTC AAGTCTTTAG AGCAAGTGAG GAAGATCCAG
480

GGCGATGGCG CAGCGCTCCA GGAGAAGCTG TGTGCCACCT AATAA
525

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

ATGGCTCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC CGACTTTGCC
60

ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
120

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
180

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
240

TCTGGCGGCT CTGGCGGCTC TCAGAGCTTC CTGCTCAAGT CTTTAGAGCA AGTGAGGAAG
300

ATCCAGGGCG ATGGCGCAGC GCTCCAGGAG AAGCTGTGTG CCACCTACAA GCTGTGCCAC
360

CCCGAGGAGC TGGTGCTGCT CGGACACTCT CTGGGCATCC CCTGGGCTCC CCTGAGCTCC
420

TGCCCCAGCC AGGCCCTGCA GCTGGCAGGC TGCTTGAGCC AACTCCATAG CGGCCTTTTC
480

CTCTACCAGG GGCTCCTGCA GGCCCTGGAA GGGATATCCT AATAA
525

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

ATGGCTATGG CCCCTGCCCT GCAGCCCACC CAGGGTGCCA TGCCGGCCTT CGCCTCTGCT
60

TTCCAGCGCC GGGCAGGAGG GGTCCTGGTT GCTAGCCATC TGCAGAGCTT CCTGGAGGTG
120

TCGTACCGCG TTCTACGCCA CCTTGCGCAG CCCTCTGGCG GCTCTGGCGG CTCTCAGAGC
180

TTCCTGCTCA AGTCTTTAGA GCAAGTGAGG AAGATCCAGG GCGATGGCGC AGCGCTCCAG
240

GAGAAGCTGT GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGCT GCTCGGACAC
300

TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT GCAGCTGGCA
360

GGCTGCTTGA GCCAACTCCA TAGCGGCCTT TTCCTCTACC AGGGGCTCCT GCAGGCCCTG
420

GAAGGGATAT CCCCCGAGTT GGGTCCCACC TTGGACACAC TGCAGCTGGA CGTCGCCGAC
480

TTTGCCACCA CCATCTGGCA GCAGATGGAA GAACTGGGAT AATAA
525

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

ATGGCTACCC AGGGTGCCAT GCCGGCCTTC GCCTCTGCTT TCCAGCGCCG GGCAGGAGGG
60

GTCCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT CGTACCGCGT TCTACGCCAC
120

CTTGCGCAGC CCTCTGGCGG CTCTGGCGGC TCTCAGAGCT TCCTGCTCAA GTCTTTAGAG
180

CAAGTGAGGA AGATCCAGGG CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAC
240

AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
300

CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT
360

AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
420

GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC CATCTGGCAG
480

CAGATGGAAG AACTGGGAAT GGCCCCTGCC CTGCAGCCCT AATAA
525

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

ATGGCTTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC
60

TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCTCTGG CGGCTCTGGC
120

GGCTCTCAGA GCTTCCTGCT CAAGTCTTTA GAGCAAGTGA GGAAGATCCA GGGCGATGGC
180

GCAGCGCTCC AGGAGAAGCT GTGTGCCACC TACAAGCTGT GCCACCCCGA GGAGCTGGTG
240

CTGCTCGGAC ACTCTCTGGG CATCCCCTGG GCTCCCCTGA GCTCCTGCCC CAGCCAGGCC
300

CTGCAGCTGG CAGGCTGCTT GAGCCAACTC CATAGCGGCC TTTTCCTCTA CCAGGGGCTC
360

CTGCAGGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA CCTTGGACAC ACTGCAGCTG
420

GACGTCGCCG ACTTTGCCAC CACCATCTGG CAGCAGATGG AAGAACTGGG AATGGCCCCT
480

GCCCTGCAGC CCACCCAGGG TGCCATGCCG GCCTTCGCCT AATAA
525

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

ATGGCTTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
60

CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC
120

CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
180

CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC
240

ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
300

ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT
360

CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC ACCTTGCGCA GCCCACACCA
420

TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA
480

AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

ATGGCTCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC CGACTTTGCC
60

ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
120

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
180

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
240

ACACCATTGG GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
300

GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC CACCTACAAG
360

CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC TGGGCATCCC CTGGGCTCCC
420

CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG CTGGCAGGCT GCTTGAGCCA ACTCCATAGC
480

GGCCTTTTCC TCTACCAGGG GCTCCTGCAG GCCCTGGAAG GGATATCCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (Synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

ATGGCTATGG CCCCTGCCCT GCAGCCCACC CAGGGTGCCA TGCCGGCCTT CGCCTCTGCT
60

TTCCAGCGCC GGGCAGGAGG GGTCCTGGTT GCTAGCCATC TGCAGAGCTT CCTGGAGGTG
120

TCGTACCGCG TTCTACGCCA CCTTGCGCAG CCCACACCAT TGGGCCCTGC CAGCTCCCTG
180

CCCCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA
240

GCGCTCCAGG AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
300

CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG
360

CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG
420

CAGGCCCTGG AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
480

GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGATA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

ATGGCTACCC AGGGTGCCAT GCCGGCCTTC GCCTCTGCTT TCCAGCGCCG GGCAGGAGGG
60

GTCCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT CGTACCGCGT TCTACGCCAC
120

CTTGCGCAGC CCACACCATT GGGCCCTGCC AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG
180

TCTTTAGAGC AAGTGAGAAA GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT
240

GCCACCTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
300

CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC
360

CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
420

CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC
480

ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

ATGGCTTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC
60

TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCACACC ATTGGGCCCT
120

GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC AAGTCTTTAG AGCAAGTGAG AAAGATCCAG
180

GGCGATGGCG CAGCGCTCCA GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG
240

GAGCTGGTGC TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
300

AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT TTTCCTCTAC
360

CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT TGGGTCCCAC CTTGGACACA
420

CTGCAGCTGG ACGTCGCCGA CTTTGCCACC ACCATCTGGC AGCAGATGGA AGAACTGGGA
480

ATGGCCCCTG CCCTGCAGCC CACCCAGGGT GCCATGCCGG CCTTCGCCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 531 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC CGACTTTGCC
60

ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
120

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
180

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
240

ACACCATTGG GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
300

GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC CACCTACAAG
360

CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC TGGGCATCCC CTGGGCTCCC
420

CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG CTGGCAGGCT GCTTGAGCCA ACTCCATAGC
480

GGCCTTTTCC TCTACCAGGG GCTCCTGCAG GCCCTGGAAG GGATATCCTA A
531

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 531 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT TGCATCTGCT
60

TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC TGCAGAGCTT CCTGGAGGTG
120

TCGTACCGCG TTCTACGCCA CCTTGCGCAG CCCACACCAT TGGGCCCTGC CAGCTCCCTG
180

CCCCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA
240

GCGCTCCAGG AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
300

CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG
360

CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG
420

CAGGCCCTGG AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
480

GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGATA A
531

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 531 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG TGCAGGTGGT
60

GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT CGTACCGCGT TCTACGCCAC
120

CTTGCGCAGC CCACACCATT GGGCCCTGCC AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG
180

TCTTTAGAGC AAGTGAGAAA GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT
240

GCCACCTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
300

CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC
360

CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC AGGCCCTGGA AGGGATATCC
420

CCCGAGTTGG GTCCCACCTT GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC
480

ATCTGGCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCTA A
531

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 531 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA TCTGCAGAGC
60

TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCACACC ATTGGGCCCT
120

GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC AAGTCTTTAG AGCAAGTGAG AAAGATCCAG
180

GGCGATGGCG CAGCGCTCCA GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG
240

GAGCTGGTGC TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
300

AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT TTTCCTCTAC
360

CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT TGGGTCCCAC CTTGGACACA
420

CTGCAGCTGG ACGTCGCCGA CTTTGCCACC ACCATCTGGC AGCAGATGGA AGAACTGGGA
480

ATGGCCCCTG CCCTGCAGCC CACCCAGGGT GCCATGCCGG CCTTCGCCTA A
531

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC CGACTTTGCC
60

ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
120

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
180

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
240

TCTGGCGGCT CTGGCGGCTC TCAGAGCTTC CTGCTCAAGT CTTTAGAGCA AGTGAGAAAG
300

ATCCAGGGCG ATGGCGCAGC GCTCCAGGAG AAGCTGTGTG CCACCTACAA GCTGTGCCAC
360

CCCGAGGAGC TGGTGCTGCT CGGACACTCT CTGGGCATCC CCTGGGCTCC CCTGAGCTCC
420

TGCCCCAGCC AGGCCCTGCA GCTGGCAGGC TGCTTGAGCC AACTCCATAG CGGCCTTTTC
480

CTCTACCAGG GGCTCCTGCA GGCCCTGGAA GGGATATCCT AA
522

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT TGCATCTGCT
60

TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC TGCAGAGCTT CCTGGAGGTG
120

TCGTACCGCG TTCTACGCCA CCTTGCGCAG CCCTCTGGCG GCTCTGGCGG CTCTCAGAGC
180

TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG GCGATGGCGC AGCGCTCCAG
240

GAGAAGCTGT GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGCT GCTCGGACAC
300

TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT GCAGCTGGCA
360

GGCTGCTTGA GCCAACTCCA TAGCGGCCTT TTCCTCTACC AGGGGCTCCT GCAGGCCCTG
420

GAAGGGATAT CCCCCGAGTT GGGTCCCACC TTGGACACAC TGCAGCTGGA CGTCGCCGAC
480

TTTGCCACCA CCATCTGGCA GCAGATGGAA GAACTGGGAT AA
522

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG TGCAGGTGGT
60

GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT CGTACCGCGT TCTACGCCAC
120

CTTGCGCAGC CCTCTGGCGG CTCTGGCGGC TCTCAGAGCT TCCTGCTCAA GTCTTTAGAG
180

CAAGTGAGAA AGATCCAGGG CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAC
240

AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
300

CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT
360

AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
420

GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC CATCTGGCAG
480

CAGATGGAAG AACTGGGAAT GGCCCCTGCC CTGCAGCCCT AA
522

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA TCTGCAGAGC
60

TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCTCTGG CGGCTCTGGC
120

GGCTCTCAGA GCTTCCTGCT CAAGTCTTTA GAGCAAGTGA GAAAGATCCA GGGCGATGGC
180

GCAGCGCTCC AGGAGAAGCT GTGTGCCACC TACAAGCTGT GCCACCCCGA GGAGCTGGTG
240

CTGCTCGGAC ACTCTCTGGG CATCCCCTGG GCTCCCCTGA GCTCCTGCCC CAGCCAGGCC
300

CTGCAGCTGG CAGGCTGCTT GAGCCAACTC CATAGCGGCC TTTTCCTCTA CCAGGGGCTC
360

CTGCAGGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA CCTTGGACAC ACTGCAGCTG
420

GACGTCGCCG ACTTTGCCAC CACCATCTGG CAGCAGATGG AAGAACTGGG AATGGCCCCT
480

GCCCTGCAGC CCACCCAGGG TGCCATGCCG GCCTTCGCCT AA
522

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
1 5 10 15

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
20 25 30

Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
35 40 45

Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
50 55 60

```
Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
65                  70                  75                  80

Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln
                85                  90                  95

Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
            100                 105                 110

Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg
        115                 120                 125

Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln
    130                 135                 140

Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
145                 150                 155                 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

```
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
1               5                   10                  15

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
            20                  25                  30

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
        35                  40                  45

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
    50                  55                  60

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly
65                  70                  75                  80

Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
                85                  90                  95
```

Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala
100 105 110

Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
115 120 125

Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu
130 135 140

Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr
145 150 155 160

Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
165 170

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
1 5 10 15

Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser
20 25 30

Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly
35 40 45

Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln
50 55 60

Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu
65 70 75 80

Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
85 90 95

Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly
100 105 110

Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu
115 120 125

Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
130 135 140

Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met
145 150 155 160

Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
165 170

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 118 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

TGGAATAAAA AAGAGAGAAG GAAAAGGATA GAAGAAGGGG GGGGAAGGGA GAAAAGGCAA
60

TTCGGAGGTA ACGAAGAAGC GGTGGGAAGG GGTATGAAAA AAATTTGGTG GGTAAAAG
118

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
1 5 10 15

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
20 25 30

Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu
35 40 45

```
Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
    50                  55                  60

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
65                  70                  75                  80

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
                85                  90                  95

Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu
            100                 105                 110

Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
        115                 120                 125

Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala
    130                 135                 140

Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu
145                 150                 155                 160

Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

```
Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
1               5                   10                  15

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
            20                  25                  30

Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
        35                  40                  45

Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
    50                  55                  60

Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
65                  70                  75                  80
```

Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln
85 90 95

Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
100 105 110

Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg
115 120 125

Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser
130 135 140

Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile
145 150 155 160

Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
165 170

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
1 5 10 15

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
20 25 30

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
35 40 45

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
50 55 60

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro
65 70 75 80

Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
85 90 95

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
100 105 110

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
115 120 125

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
130 135 140

Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu
145 150 155 160

Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
165 170

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
1 5 10 15

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
20 25 30

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
35 40 45

Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
50 55 60

Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
65 70 75 80

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
85 90 95

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
100 105 110

Cys Pr Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
115 120 125

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
130 135 140

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
145 150 155 160

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
165 170

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
1 5 10 15

Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser
20 25 30

Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala
35 40 45

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg
50 55 60

Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
65 70 75 80

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
85 90 95

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
100 105 110

Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
115 120 125

Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
130 135 140

Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
145 150 155 160

Gln Gln Met Glu Glu Leu Gly Met Ala Pr Ala Leu Gln Pro
165 170

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

```
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
1               5                  10                  15

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
            20                  25                  30

Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
        35                  40                  45

Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
    50                  55                  60

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
65                  70                  75                  80

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
                85                  90                  95

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
            100                 105                 110

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
        115                 120                 125

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
    130                 135                 140

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
145                 150                 155                 160

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amin acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

```
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
1               5                  10                  15

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
            20                  25                  30

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
        35                  40                  45

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
    50                  55                  60

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro
65                  70                  75                  80

Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
                85                  90                  95

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
            100                 105                 110

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
        115                 120                 125

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
    130                 135                 140

Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu
145                 150                 155                 160

Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: pr tein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

```
Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
1               5                  10                  15

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
            20                  25                  30

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
        35                  40                  45

Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
    50                  55                  60

Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
65                  70                  75                  80

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
                85                  90                  95

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
            100                 105                 110

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
        115                 120                 125

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
    130                 135                 140

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
145                 150                 155                 160

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

```
Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
1               5                  10                  15
```

Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser
20 25 30

Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala
35 40 45

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg
50 55 60

Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
65 70 75 80

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
85 90 95

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
100 105 110

Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
115 120 125

Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
130 135 140

Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
145 150 155 160

Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
165 170

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
1 5 10 15

Gln Ser Ph Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
20 25 30

Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
35 40 45

```
Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
    50                  55                  60

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
65                  70                  75                  80

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
                85                  90                  95

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
            100                 105                 110

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
        115                 120                 125

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
    130                 135                 140

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
145                 150                 155                 160

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

```
Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
1               5                   10                  15

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
            20                  25                  30

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
        35                  40                  45

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
    50                  55                  60

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly
65                  70                  75                  80
```

Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
85 90 95

Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala
100 105 110

Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
115 120 125

Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu
130 135 140

Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr
145 150 155 160

Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
165 170

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 169 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
1 5 10 15

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
20 25 30

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
35 40 45

Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu
50 55 60

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
65 70 75 80

Ala Thr Tyr Lys Leu Cys His Pr Glu Glu Leu Val Leu L u Gly His
85 90 95

Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala
100 105 110

Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu
115 120 125

Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly
130 135 140

Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr
145 150 155 160

Ile Trp Gln Gln Met Glu Glu Leu Gly
165

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
1 5 10 15

Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser
20 25 30

Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly
35 40 45

Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln
50 55 60

Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu
65 70 75 80

Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
85 90 95

Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly
100 105 110

Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu
115 120 125

Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr
130 135 140

Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met
145 150 155 160

Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
165 170

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu
1 5 10 15

Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
20 25 30

Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu
35 40 45

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
50 55 60

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
65 70 75 80

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser
85 90 95

Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu
100 105 110

Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
115 120 125

Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala
130 135 140

Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu
145 150 155 160

Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
165 170

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Gly Gly Gly Ser Gly Gly Gly Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Ser Gly Gly Ser Gly Gly Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Glu Phe Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Glu Phe Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Glu Phe Gly Gly Asn Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Gly Gly Ser Asp Met Ala Gly
1 5

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

GATCGACCAT GGCTCTGCTC GGACACTCTC TG
32

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

CGATCGAAGC TTATTACACC AGCTCCTCGG GGTGGC
36

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

GATCGACCAT GGCTCAACTC CATAGCGGCC TT
32

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

CGATCGAAGC TTATTAGCTC AAGCAGCCTG CCAGCT
36

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

GATCGACCAT GGCTCTTTTC CTCTACCAGG GG
32

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

CGATCGAAGC TTATTAGCCG CTATGGAGTT GGCTCA
36

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

GATCGACCAT GGCTCTCTAC CAGGGGCTCC TG
32

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

CGATCGAAGC TTATTAGAAA AGGCCGCTAT GGAGTT
36

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

GATCGACCAT GGCTGCCCTG GAAGGGATAT CC
32

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

CGATCGAAGC TTATTACTGC AGGAGCCCCT GGTAGA
36

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

GATCGACCAT GGCTGACTTT GCCACCACCA TC
32

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

CGATCGAAGC TTATTAGGCG ACGTCCAGCT GCAGTG
36

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

GATCGACCAT GGCTATCTGG CAGCAGATGG AA
32

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

CGATCGAAGC TTATTAGGTG GTGGCAAAGT CGGCGA
36

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

GATCGACCAT GGCTCAGCAG ATGGAAGAAC TG
32

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

CGATCGAAGC TTATTACCAG ATGGTGGTGG CAAAGT
36

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

CATGGCTTTG TTAGGACATT CTTTAGGTAT TCCATGGGCT CCTCTGAGCT
50

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

CAGAGGAGCC CATGGAATAC CTAAAGAATG TCCTAACAAA
40

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

ATGGCTCTGC TCGGACACTC TCTGGGCATC CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC
60

CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG
120

GGGCTCCTGC AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
180

CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA ACTGGGAATG
240

GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC
300

CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC
360

GTTCTACGCC ACCTTGCGCA GCCCACACCA TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC
420

TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG GCGATGGCGC AGCGCTCCAG
480

GAGAAGCTGT GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

ATGGCTCAAC TCCATAGCGG CCTTTTCCTC TACCAGGGGC TCCTGCAGGC CCTGGAAGGG
60

ATATCCCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC CGACTTTGCC
120

ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
180

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
240

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
300

ACACCATTGG GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
360

GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC CACCTACAAG
420

CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC TGGGCATCCC CTGGGCTCCC
480

CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG CTGGCAGGCT GCTTGAGCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

ATGGCTCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
60

GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC CATCTGGCAG
120

CAGATGGAAG AACTGGGAAT GGCCCCTGCC CTGCAGCCCA CCCAGGGTGC CATGCCGGCC
180

TTCGCCTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC
240

TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC AGCCCACACC ATTGGGCCCT
300

GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC AAGTCTTTAG AGCAAGTGAG AAAGATCCAG
360

GGCGATGGCG CAGCGCTCCA GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG
420

GAGCTGGTGC TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
480

AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

ATGGCTCTCT ACCAGGGGCT CCTGCAGGCC CTGGAAGGGA TATCCCCCGA GTTGGGTCCC
60

ACCTTGGACA CACTGCAGCT GGACGTCGCC GACTTTGCCA CCACCATCTG GCAGCAGATG
120

GAAGAACTGG GAATGGCCCC TGCCCTGCAG CCCACCCAGG GTGCCATGCC GGCCTTCGCC
180

TCTGCTTTCC AGCGCCGGGC AGGAGGGGTC CTGGTTGCTA GCCATCTGCA GAGCTTCCTG
240

GAGGTGTCGT ACCGCGTTCT ACGCCACCTT GCGCAGCCCA CACCATTGGG CCCTGCCAGC
300

TCCCTGCCCC AGAGCTTCCT GCTCAAGTCT TTAGAGCAAG TGAGAAAGAT CCAGGGCGAT
360

GGCGCAGCGC TCCAGGAGAA GCTGTGTGCC ACCTACAAGC TGTGCCACCC CGAGGAGCTG
420

GTGCTGCTCG GACACTCTCT GGGCATCCCC TGGGCTCCCC TGAGCTCCTG CCCCAGCCAG
480

GCCCTGCAGC TGGCAGGCTG CTTGAGCCAA CTCCATAGCG GCCTTTTCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

ATGGCTGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA CCTTGGACAC ACTGCAGCTG
60

GACGTCGCCG ACTTTGCCAC CACCATCTGG CAGCAGATGG AAGAACTGGG AATGGCCCCT
120

GCCCTGCAGC CCACCCAGGG TGCCATGCCG GCCTTCGCCT CTGCTTTCCA GCGCCGGGCA
180

GGAGGGGTCC TGGTTGCTAG CCATCTGCAG AGCTTCCTGG AGGTGTCGTA CCGCGTTCTA
240

CGCCACCTTG CGCAGCCCAC ACCATTGGGC CCTGCCAGCT CCCTGCCCCA GAGCTTCCTG
300

CTCAAGTCTT TAGAGCAAGT GAGAAAGATC CAGGGCGATG GCGCAGCGCT CCAGGAGAAG
360

CTGTGTGCCA CCTACAAGCT GTGCCACCCC GAGGAGCTGG TGCTGCTCGG ACACTCTCTG
420

GGCATCCCCT GGGCTCCCCT GAGCTCCTGC CCCAGCCAGG CCCTGCAGCT GGCAGGCTGC
480

TTGAGCCAAC TCCATAGCGG CCTTTTCCTC TACCAGGGGC TCCTGCAGTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

ATGGCTGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT GGCCCCTGCC
60

CTGCAGCCCA CCCAGGGTGC CATGCCGGCC TTCGCCTCTG CTTTCCAGCG CCGGGCAGGA
120

GGGGTCCTGG TTGCTAGCCA TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC
180

CACCTTGCGC AGCCCACACC ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC
240

AAGTCTTTAG AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA GGAGAAGCTG
300

TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC TGCTCGGACA CTCTCTGGGC
360

ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG
420

AGCCAACTCC ATAGCGGCCT TTTCCTCTAC CAGGGGCTCC TGCAGGCCCT GGAAGGGATA
480

TCCCCCGAGT TGGGTCCCAC CTTGGACACA CTGCAGCTGG ACGTCGCCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

ATGGCTATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC CTGCCCTGCA GCCCACCCAG
60

GGTGCCATGC CGGCCTTCGC CTCTGCTTTC CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT
120

AGCCATCTGC AGAGCTTCCT GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC
180

ACACCATTGG GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
240

GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC CACCTACAAG
300

CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC TGGGCATCCC CTGGGCTCCC
360

CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG CTGGCAGGCT GCTTGAGCCA ACTCCATAGC
420

GGCCTTTTCC TCTACCAGGG GCTCCTGCAG GCCCTGGAAG GGATATCCCC CGAGTTGGGT
480

CCCACCTTGG ACACACTGCA GCTGGACGTC GCCGACTTTG CCACCACCTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

ATGGCTCAGC AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
60

ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT
120

CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC ACCTTGCGCA GCCCACACCA
180

TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA
240

AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA CAAGCTGTGC
300

CACCCCGAGG AGCTGGTGCT GCTCGGACAC TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC
360

TCCTGCCCCA GCCAGGCCCT GCAGCTGGCA GGCTGCTTGA GCCAACTCCA TAGCGGCCTT
420

TTCCTCTACC AGGGGCTCCT GCAGGCCCTG GAAGGGATAT CCCCCGAGTT GGGTCCCACC
480

TTGGACACAC TGCAGCTGGA CGTCGCCGAC TTTGCCACCA CCATCTGGTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "DNA (synthetic)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

ATGGCTTTGT TAGGACATTC TTTAGGTATT CCATGGGCTC CTCTGAGCTC CTGCCCCAGC
60

CAGGCCCTGC AGCTGGCAGG CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG
120

GGGCTCCTGC AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
180

CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA ACTGGGAATG
240

GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC
300

CGGGCAGGAG GGGTCCTGGT TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC
360

GTTCTACGCC ACCTTGCGCA GCCCACACCA TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC
420

TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG GCGATGGCGC AGCGCTCCAG
480

GAGAAGCTGT GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGTA ATAA
534

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amin acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

```
Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys
1               5                  10                  15

Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
            20                  25                  30

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
        35                  40                  45

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
    50                  55                  60

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
65                  70                  75                  80

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
                85                  90                  95

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
            100                 105                 110

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro
        115                 120                 125

Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
    130                 135                 140

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
145                 150                 155                 160

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu
1 5 10 15

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
20 25 30

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu
35 40 45

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
50 55 60

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
65 70 75 80

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala
85 90 95

Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu
100 105 110

Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
115 120 125

Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu
130 135 140

Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser
145 150 155 160

Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser
165 170

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro
1 5 10 15

```
Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
            20                  25                  30

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala
        35                  40                  45

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln
    50                  55                  60

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu
65                  70                  75                  80

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu
                85                  90                  95

Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu
            100                 105                 110

Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
        115                 120                 125

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly
    130                 135                 140

His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln
145                 150                 155                 160

Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

```
Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu
1               5                   10                  15

Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr
            20                  25                  30

Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln
        35                  40                  45
```

Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
50 55 60

Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val
65 70 75 80

Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro
85 90 95

Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val
100 105 110

Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala
115 120 125

Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
130 135 140

Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu
145 150 155 160

Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe
165 170

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu
1 5 10 15

Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu
20 25 30

Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro
35 40 45

Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala
50 55 60

Ser His Leu Gln Ser Phe Leu Glu Val S r Tyr Arg Val Leu Arg His
65 70 75 80

Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
85 90 95

Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
100 105 110

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro
115 120 125

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro
130 135 140

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser
145 150 155 160

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
165 170

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
1 5 10 15

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
20 25 30

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
35 40 45

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr
50 55 60

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser
65 70 75 80

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
85 90 95

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu
100 105 110

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
115 120 125

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
130 135 140

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro
145 150 155 160

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
165 170

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
1 5 10 15

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala
20 25 30

Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser
35 40 45

Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala
50 55 60

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg
65 70 75 80

Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
85 90 95

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
100 105 110

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pr Ser Gln Ala Leu Gln
115 120 125

Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
130 135 140

```
Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
145                 150                 155                 160

Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

```
Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln
1               5                   10                  15

Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
            20                  25                  30

Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg
        35                  40                  45

Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser
    50                  55                  60

Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile
65                  70                  75                  80

Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys
                85                  90                  95

Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile
            100                 105                 110

Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
        115                 120                 125

Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu
    130                 135                 140

Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp
145                 150                 155                 160

Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
                165                 170
```

(2) INFORMATION FOR SEQ ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

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Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys
1               5                  10                  15

Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
            20                  25                  30

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser
        35                  40                  45

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp
    50                  55                  60

Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro
65                  70                  75                  80

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
                85                  90                  95

Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
            100                 105                 110

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro
        115                 120                 125

Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
    130                 135                 140

Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
145                 150                 155                 160

Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
                165                 170
```

WHAT IS CLAIMED IS:

1. A human G-CSF receptor agonist polypeptide, comprising a modified G-CSF amino acid sequence of the Formula:

1 10
Xaa Xaa Xaa Gly Pro Ala Ser Ser Leu Pro Gln Ser Xaa

20
Leu Leu Xaa Xaa Xaa Glu Gln Val Xaa Lys Xaa Gln Gly Xaa Gly

30 40
Ala Xaa Leu Gln Glu Xaa Leu Xaa Ala Thr Tyr Lys Leu Xaa Xaa

50
Xaa Glu Xaa Xaa Val Xaa Xaa Gly His Ser Xaa Gly Ile Pro Trp

60 70
Ala Pro Leu Ser Ser Xaa Pro Ser Xaa Ala Leu Xaa Leu Ala Gly

80
Xaa Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu

90 100
Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu

110
Xaa Thr Leu Gln Xaa Asp Val Ala Asp Phe Ala Xaa Thr Ile Trp

120 130
Gln Gln Met Glu Xaa Xaa Gly Met Ala Pro Ala Leu Gln Pro Thr

140
Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Xaa Gln Xaa Xaa Ala

150 160
Gly Gly Val Leu Val Ala Ser Xaa Leu Gln Xaa Phe Leu Xaa Xaa

170
Ser Tyr Arg Val Leu Xaa Xaa Leu Ala Gln Pro (SEQ ID NO:1)

wherein

Xaa at position 1 is Thr, Ser, Arg, Tyr or Gly;
Xaa at position 2 is Pro or Leu;
Xaa at position 3 is Leu, Arg, Tyr or Ser;
Xaa at position 13 is Phe, Ser, His, Thr or Pro;
Xaa at position 16 is Lys, Pro, Ser, Thr or His;

Xaa at position 17 is Cys, Ser, Gly, Ala, Ile, Tyr or Arg;
Xaa at position 18 is Leu, Thr, Pro, His, Ile or Cys;
Xaa at position 22 is Arg, Tyr, Ser, Thr or Ala;
Xaa at position 24 is Ile, Pro, Tyr or Leu;
Xaa at position 27 is Asp, or Gly;
Xaa at position 30 is Ala, Ile, Leu or Gly;
Xaa at position 34 is Lys or Ser;
Xaa at position 36 is Cys or Ser;
Xaa at position 42 is Cys or Ser;
Xaa at position 43 is His, Thr, Gly, Val, Lys, Trp, Ala, Arg, Cys, or Leu;
Xaa at position 44 is Pro, Gly, Arg, Asp, Val, Ala, His, Trp, Gln, or Thr;
Xaa at position 46 is Glu, Arg, Phe, Arg, Ile or Ala;
Xaa at position 47 is Leu or Thr;
Xaa at position 49 is Leu, Phe, Arg or Ser;
Xaa at position 50 is Leu, Ile, His, Pro or Tyr;
Xaa at position 54 is Leu or His;
Xaa at position 64 is Cys or Ser;
Xaa at position 67 is Gln, Lys, Leu or Cys;
Xaa at position 70 is Gln, Pro, Leu, Arg or Ser;
Xaa at position 74 is Cys or Ser;
Xaa at position 104 is Asp, Gly or Val;
Xaa at position 108 is Leu, Ala, Val, Arg, Trp, Gln or Gly;
Xaa at position 115 is Thr, His, Leu or Ala;
Xaa at position 120 is Gln, Gly, Arg, Lys or His
Xaa at position 123 is Glu, Arg, Phe or Thr
Xaa at position 144 is Phe, His, Arg, Pro, Leu, Gln or Glu;
Xaa at position 146 is Arg or Gln;
Xaa at position 147 is Arg or Gln;
Xaa at position 156 is His, Gly or Ser;
Xaa at position 159 is Ser, Arg, Thr, Tyr, Val or Gly;
Xaa at position 162 is Glu, Leu, Gly or Trp;
Xaa at position 163 is Val, Gly, Arg or Ala;
Xaa at position 169 is Arg, Ser, Leu, Arg or Cys;
Xaa at position 170 is His, Arg or Ser;

wherein optionally 1-11 amino acids from the N-terminus and 1-5 from the C-terminus can be deleted;

wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-terminus at amino acids;

38-39	62-63	123-124
39-40	63-64	124-125
40-41	64-65	125-126
41-42	65-66	126-127

42-43	66-67	128-129
43-44	67-68	128-129
45-46	68-69	129-130
48-49	69-70	130-131
49-50	70-71	131-132
52-53	71-72	132-133
53-54	91-92	133-134
54-55	92-93	134-135
55-56	93-94	135-136
56-57	94-95	136-137
57-58	95-96	137-138
58-59	96-97	138-139
59-60	97-98	139-140
60-61	98-99	140-141
61-62	99-100	141-142
		or 142-143; and

said G-CSF receptor agonist polypeptide may optionally be immediately preceded by (methionine^{-1}), (alanine^{-1}) or (methionine^{-2}, alanine^{-1}).

2. The G-CSF receptor agonist polypeptide, as recited in claim 1, wherein said linker is selected from the group consisting of;

GlyGlyGlySer (SEQ ID NO:2);
GlyGlyGlySerGlyGlyGlySer (SEQ ID NO:61);
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer (SEQ ID NO:62);
SerGlyGlySerGlyGlySer (SEQ ID NO:63);
GluPheGlyAsnMet (SEQ ID NO:64);
GluPheGlyGlyAsnMet (SEQ ID NO:65);
GluPheGlyGlyAsnGlyGlyAsnMet (SEQ ID NO:66); and
GlyGlySerAspMetAlaGly (SEQ ID NO:67).

3. The G-CSF receptor agonist polypeptide of claim 1, selected from the group consisting of;

Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser
Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala
Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe
Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu
Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln
Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln
Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu
Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala
Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:48);

Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met
Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala
Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:49);

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln
Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly
Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu
Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile
Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro
Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr
Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:50);

Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg
Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu
Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu
Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu
Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:51); and

Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser
Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys
His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro
Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala
Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile
Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro
Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:52).

4. A nucleic acid molecule comprising a DNA sequence encoding the G-CSF receptor agonist polypeptide of claim 1.

5. A nucleic acid molecule comprising a DNA sequence encoding the G-CSF receptor agonist polypeptide of claim 2.

6. A nucleic acid molecule comprising a DNA sequence encoding the G-CSF receptor agonist polypeptide of claim 3.

7. A nucleic acid molecule of claim 6 selected from group consisting of;

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  1  ATGGCTTACA AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC
 51  TCTGGGCATC CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC
101  AGCTGGCAGG CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG
151  GGGCTCCTGC AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT
201  GGACACACTG CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC
251  AGATGGAAGA ACTGGGAATG GCCCCTGCCC TGCAGCCCAC CCAGGGTGCC
301  ATGCCGGCCT TCGCCTCTGC TTTCCAGCGC CGGGCAGGAG GGGTCCTGGT
351  TGCTAGCCAT CTGCAGAGCT TCCTGGAGGT GTCGTACCGC GTTCTACGCC
401  ACCTTCGCA GCCCACACCA TTGGGCCCTG CCAGCTCCCT GCCCCAGAGC
451  TTCCTGCTCA AGTCTTTAGA GCAAGTGAGA AAGATCCAGG GCGATGGCGC
501  AGCGCTCCAG GAGAAGCTGT GTGCCACCTA ATAA (SEQ ID NO:30);

  1  ATGGCTCCCG AGTTGGGTCC CACCTTGGAC ACACTGCAGC TGGACGTCGC
 51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC ACACCATTGG
251  GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
301  GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC
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 351  CACCTACAAG CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC
 401  TGGGCATCCC CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG
 451  CTGGCAGGCT GCTTGAGCCA ACTCCATAGC GGCCTTTTCC TCTACCAGGG
 501  GCTCCTGCAG GCCCTGGAAG GGATATCCTA ATAA (SEQ ID NO:31);

   1  ATGGCTATGG CCCCTGCCCT GCAGCCCACC CAGGGTGCCA TGCCGGCCTT
  51  CGCCTCTGCT TTCCAGCGCC GGGCAGGAGG GGTCCTGGTT GCTAGCCATC
 101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
 151  CCCACACCAT TGGGCCCTGC CAGCTCCCTG CCCCAGAGCT TCCTGCTCAA
 201  GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA GCGCTCCAGG
 251  AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
 301  CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG
 351  CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT
 401  TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
 451  GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC
 501  CATCTGGCAG CAGATGGAAG AACTGGGATA ATAA (SEQ ID NO:32);

   1  ATGGCTACCC AGGGTGCCAT GCCGGCCTTC GCCTCTGCTT TCCAGCGCCG
  51  GGCAGGAGGG GTCCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
 101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCACACCATT GGGCCCTGCC
 151  AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG TCTTTAGAGC AAGTGAGAAA
 201  GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT GCCACCTACA
 251  AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
 301  CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG
 351  CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC
 401  AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
 451  CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA
 501  ACTGGGAATG GCCCCTGCCC TGCAGCCCTA ATAA (SEQ ID NO:33);

   1  ATGGCTTCTG CTTTCCAGCG CCGGGCAGGA GGGGTCCTGG TTGCTAGCCA
  51  TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
 101  AGCCCACACC ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC
 151  AAGTCTTTAG AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA
 201  GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC
 251  TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
 301  AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT
 351  TTTCCTCTAC CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT
 401  TGGGTCCCAC CTTGGACACA CTGCAGCTGG ACGTCGCCGA CTTTGCCACC
 451  ACCATCTGGC AGCAGATGGA AGAACTGGGA ATGGCCCCTG CCCTGCAGCC
 501  CACCCAGGGT GCCATGCCGG CCTTCGCCTA ATAA  (SEQ ID NO:34);

   1  ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC
  51  CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
 101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
 151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
 201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC ACACCATTGG
 251  GCCCTGCCAG CTCCCTGCCC CAGAGCTTCC TGCTCAAGTC TTTAGAGCAA
 301  GTGAGAAAGA TCCAGGGCGA TGGCGCAGCG CTCCAGGAGA AGCTGTGTGC
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351  CACCTACAAG CTGTGCCACC CCGAGGAGCT GGTGCTGCTC GGACACTCTC
401  TGGGCATCCC CTGGGCTCCC CTGAGCTCCT GCCCCAGCCA GGCCCTGCAG
451  CTGGCAGGCT GCTTGAGCCA ACTCCATAGC GGCCTTTTCC TCTACCAGGG
501  GCTCCTGCAG GCCCTGGAAG GGATATCCTA A (SEQ ID NO:35);

 1   ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT
51   TGCATCTGCT TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC
101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
151  CCCACACCAT TGGGCCCTGC CAGCTCCCTG CCCCAGAGCT TCCTGCTCAA
201  GTCTTTAGAG CAAGTGAGAA AGATCCAGGG CGATGGCGCA GCGCTCCAGG
251  AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
301  CTCGGACACT CTCTGGGCAT CCCCTGGGCT CCCCTGAGCT CCTGCCCCAG
351  CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG CCAACTCCAT AGCGGCCTTT
401  TCCTCTACCA GGGGCTCCTG CAGGCCCTGG AAGGGATATC CCCCGAGTTG
451  GGTCCCACCT TGGACACACT GCAGCTGGAC GTCGCCGACT TTGCCACCAC
501  CATCTGGCAG CAGATGGAAG AACTGGGATA A (SEQ ID NO:36);

 1   ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG
51   TGCAGGTGGT GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCACACCATT GGGCCCTGCC
151  AGCTCCCTGC CCCAGAGCTT CCTGCTCAAG TCTTTAGAGC AAGTGAGAAA
201  GATCCAGGGC GATGGCGCAG CGCTCCAGGA GAAGCTGTGT GCCACCTACA
251  AGCTGTGCCA CCCCGAGGAG CTGGTGCTGC TCGGACACTC TCTGGGCATC
301  CCCTGGGCTC CCCTGAGCTC CTGCCCCAGC CAGGCCCTGC AGCTGGCAGG
351  CTGCTTGAGC CAACTCCATA GCGGCCTTTT CCTCTACCAG GGGCTCCTGC
401  AGGCCCTGGA AGGGATATCC CCCGAGTTGG GTCCCACCTT GGACACACTG
451  CAGCTGGACG TCGCCGACTT TGCCACCACC ATCTGGCAGC AGATGGAAGA
501  ACTGGGAATG GCCCCTGCCC TGCAGCCCTA A (SEQ ID NO:37);

 1   ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA
51   TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCACACC ATTGGGCCCT GCCAGCTCCC TGCCCCAGAG CTTCCTGCTC
151  AAGTCTTTAG AGCAAGTGAG AAAGATCCAG GGCGATGGCG CAGCGCTCCA
201  GGAGAAGCTG TGTGCCACCT ACAAGCTGTG CCACCCCGAG GAGCTGGTGC
251  TGCTCGGACA CTCTCTGGGC ATCCCCTGGG CTCCCCTGAG CTCCTGCCCC
301  AGCCAGGCCC TGCAGCTGGC AGGCTGCTTG AGCCAACTCC ATAGCGGCCT
351  TTTCCTCTAC CAGGGGCTCC TGCAGGCCCT GGAAGGGATA TCCCCCGAGT
401  TGGGTCCCAC CTTGGACACA CTGCAGCTGG ACGTCGCCGA CTTTGCCACC
451  ACCATCTGGC AGCAGATGGA AGAACTGGGA ATGGCCCCTG CCCTGCAGCC
501  CACCCAGGGT GCCATGCCGG CCTTCGCCTA A (SEQ ID NO:38);

 1   ATGGCTCCGG AACTGGGTCC AACTCTGGAC ACACTGCAGC TGGACGTCGC
51   CGACTTTGCC ACCACCATCT GGCAGCAGAT GGAAGAACTG GGAATGGCCC
101  CTGCCCTGCA GCCCACCCAG GGTGCCATGC CGGCCTTCGC CTCTGCTTTC
151  CAGCGCCGGG CAGGAGGGGT CCTGGTTGCT AGCCATCTGC AGAGCTTCCT
201  GGAGGTGTCG TACCGCGTTC TACGCCACCT TGCGCAGCCC TCTGGCGGCT
251  CTGGCGGCTC TCAGAGCTTC CTGCTCAAGT CTTTAGAGCA AGTGAGAAAG
301  ATCCAGGGCG ATGGCGCAGC GCTCCAGGAG AAGCTGTGTG CCACCTACAA
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351  GCTGTGCCAC CCCGAGGAGC TGGTGCTGCT CGGACACTCT CTGGGCATCC
401  CCTGGGCTCC CCTGAGCTCC TGCCCCAGCC AGGCCCTGCA GCTGGCAGGC
451  TGCTTGAGCC AACTCCATAG CGGCCTTTTC CTCTACCAGG GGCTCCTGCA
501  GGCCCTGGAA GGGATATCCT AA (SEQ ID NO:39);

 1   ATGGCTATGG CTCCAGCTCT GCAACCAACT CAAGGTGCAA TGCCAGCATT
51   TGCATCTGCT TTTCAACGTC GTGCAGGTGG TGTTCTGGTT GCTAGCCATC
101  TGCAGAGCTT CCTGGAGGTG TCGTACCGCG TTCTACGCCA CCTTGCGCAG
151  CCCTCTGGCG GCTCTGGCGG CTCTCAGAGC TTCCTGCTCA AGTCTTTAGA
201  GCAAGTGAGA AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT
251  GTGCCACCTA CAAGCTGTGC CACCCCGAGG AGCTGGTGCT GCTCGGACAC
301  TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC TCCTGCCCCA GCCAGGCCCT
351  GCAGCTGGCA GGCTGCTTGA GCCAACTCCA TAGCGGCCTT TTCCTCTACC
401  AGGGGCTCCT GCAGGCCCTG GAAGGGATAT CCCCCGAGTT GGGTCCCACC
451  TTGGACACAC TGCAGCTGGA CGTCGCCGAC TTTGCCACCA CCATCTGGCA
501  GCAGATGGAA GAACTGGGAT AA (SEQ ID NO:40);

 1   ATGGCTACTC AAGGTGCTAT GCCAGCTTTT GCTTCTGCTT TTCAACGTCG
51   TGCAGGTGGT GTTCTGGTTG CTAGCCATCT GCAGAGCTTC CTGGAGGTGT
101  CGTACCGCGT TCTACGCCAC CTTGCGCAGC CCTCTGGCGG CTCTGGCGGC
151  TCTCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGAA AGATCCAGGG
201  CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAC AAGCTGTGCC
251  ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
301  CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG
351  CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG
401  AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
451  GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT
501  GGCCCCTGCC CTGCAGCCCT AA (SEQ ID NO:41); and

 1   ATGGCTTCTG CTTTTCAACG TCGTGCAGGT GGTGTTCTGG TTGCTAGCCA
51   TCTGCAGAGC TTCCTGGAGG TGTCGTACCG CGTTCTACGC CACCTTGCGC
101  AGCCCTCTGG CGGCTCTGGC GGCTCTCAGA GCTTCCTGCT CAAGTCTTTA
151  GAGCAAGTGA GAAAGATCCA GGGCGATGGC GCAGCGCTCC AGGAGAAGCT
201  GTGTGCCACC TACAAGCTGT GCCACCCCGA GGAGCTGGTG CTGCTCGGAC
251  ACTCTCTGGG CATCCCCTGG GCTCCCCTGA GCTCCTGCCC CAGCCAGGCC
301  CTGCAGCTGG CAGGCTGCTT GAGCCAACTC CATAGCGGCC TTTTCCTCTA
351  CCAGGGGCTC CTGCAGGCCC TGGAAGGGAT ATCCCCCGAG TTGGGTCCCA
401  CCTTGGACAC ACTGCAGCTG GACGTCGCCG ACTTTGCCAC CACCATCTGG
451  CAGCAGATGG AAGAACTGGG AATGGCCCCT GCCCTGCAGC CCACCCAGGG
501  TGCCATGCCG GCCTTCGCCT AA (SEQ ID NO:42).
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8. A method of producing a G-CSF receptor agonist polypeptide comprising: growing under suitable nutrient conditions, a host cell transformed or transfected with a replicable vector comprising said nucleic acid molecule of claim 4, 5, 6 or 7 in a manner allowing expression of said

G-CSF receptor agonist polypeptide and recovering said G-CSF receptor agonist polypeptide.

9. A composition comprising; a G-CSF receptor agonist polypeptide according to claim 1, 2, or 3; and a pharmaceutically acceptable carrier.

10. A composition comprising; a G-CSF receptor agonist polypeptide according to claim 1, 2, or 3; a colony stimulating factor; and a pharmaceutically acceptable carrier.

11. A composition comprising; a G-CSF receptor agonist polypeptide according to claim 1, 2, or 3; a colony stimulating factor selected from the group consisting of:

GM-CSF, c-mpl ligand, M-CSF, erythropoietin, IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor; and

a pharmaceutically acceptable carrier.

12. A method of stimulating the production of hematopoietic cells in a patient comprising the step of; administering said G-CSF receptor agonist polypeptide of claim 1, 2, or 3 to said patent.

13. A method of stimulating the production of hematopoietic cells in a patient comprising the step of administering said composition of claim 9, 10 or 11 to said patient.

14. A method for selective ex vivo expansion of stem cells, comprising the steps of; (a) separating stem cells from other cells; (b) culturing said separated stem cells with a selected culture medium comprising the polypeptide of claim 1, 2, or 3; and

(c) harvesting said cultured cells.

15. A method for selective ex vivo expansion of stem cells, comprising the steps of; (a) separating stem cells from other cells; (b) culturing said separated stem cells with a selected culture medium comprising the composition of claim 9, 10 or 11; and

(c) harvesting said cultured cells.

16. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of; (a) removing stem cells; (b) separating stem cells from other cells; (c) culturing said separated stem cells with a selected culture medium comprising the polypeptide of claim 1, 2, or 3;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said patient.

17. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of; (a) removing stem cells; (b) separating stem cells from other cells; (c) culturing said separated stem cells with a selected culture medium comprising the composition of claim 9;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said patient.

18. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of; (a) removing stem cells; (b) separating stem cells from other cells; (c) culturing said separated stem cells with a selected culture medium comprising the composition of claim 10;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said patient.

19. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of; (a) removing stem cells; (b) separating stem cells from other cells; (c) culturing said separated stem cells with a selected culture medium comprising the composition of claim 11;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said patient.

20. A method of human gene therapy, comprising the steps of;

(a) removing stem cells from a patient;

(b) separating said stem cells from other cells;

(c) culturing said separated stem cells with a selected culture medium comprising the hematopoietic protein of claim 1, 2, or 3;

(d) introducing DNA into said cultured cells;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

21. A method of human gene therapy, comprising the steps of;

(a) removing stem cells from a patient;

(b) separating said stem cells from other cells;

(c) culturing said separated stem cells with a selected

media comprising the composition of claim 9;

(d) introducing DNA into said cultured cells;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

22. A method of human gene therapy, comprising the steps of;

(a) removing stem cells from a patient;

(b) separating said stem cells from other cells;

(c) culturing said separated stem cells with a selected

media comprising the composition of claim 10;

(d) introducing DNA into said cultured cells;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

23. A method of human gene therapy, comprising the steps of;

(a) removing stem cells from a patient;

(b) separating said stem cells from other cells;

(c) culturing said separated stem cells with a selected

media comprising the composition of claim 11;

(d) introducing DNA into said cultured cells;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

24. A method of claim 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 wherein said stem cells are isolated from peripheral blood.

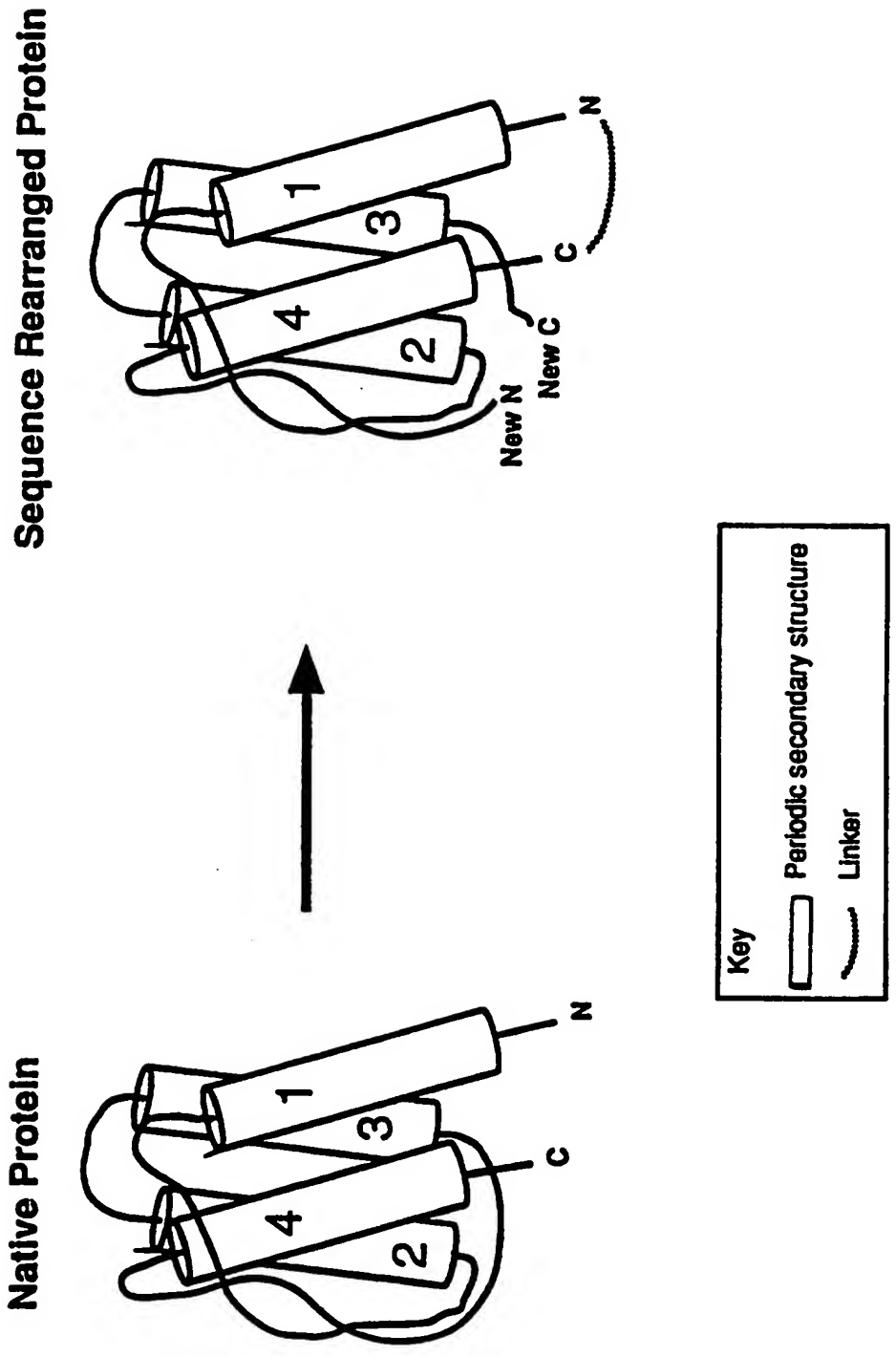

Native Protein
Sequence Rearranged Protein
1
2
3
4
N
C
New N
New C
Key
Periodic secondary structure
Linker

Figure 1

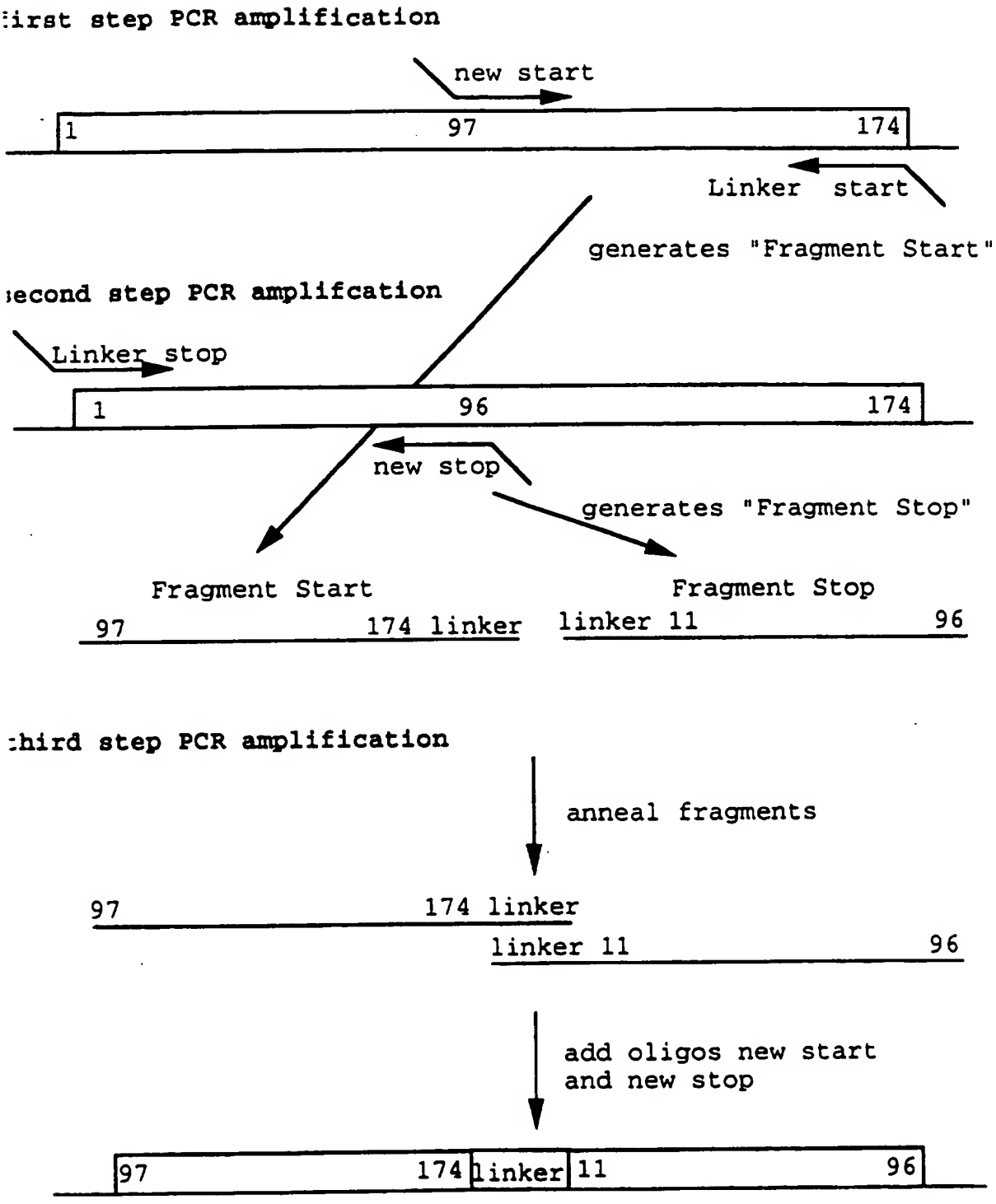

first step PCR amplification
new start
1
97
174
Linker start
generates "Fragment Start"
second step PCR amplifcation
Linker stop
1
96
174
new stop
generates "Fragment Stop"
Fragment Start
97
174 linker
Fragment Stop
linker 11
96
third step PCR amplification
anneal fragments
97
174 linker
linker 11
96
add oligos new start
and new stop
97
174
linker
11
96

Figure 2.

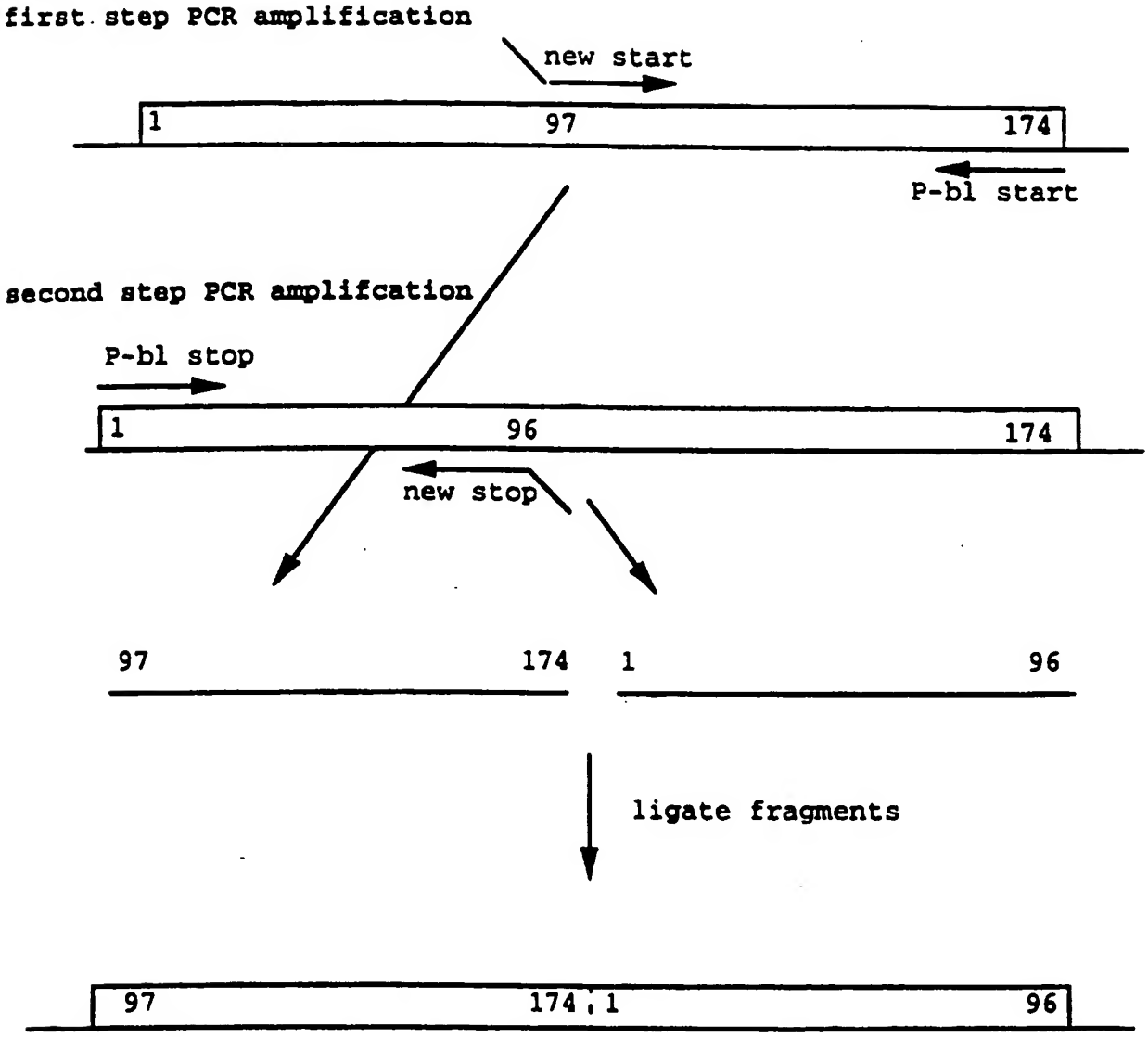
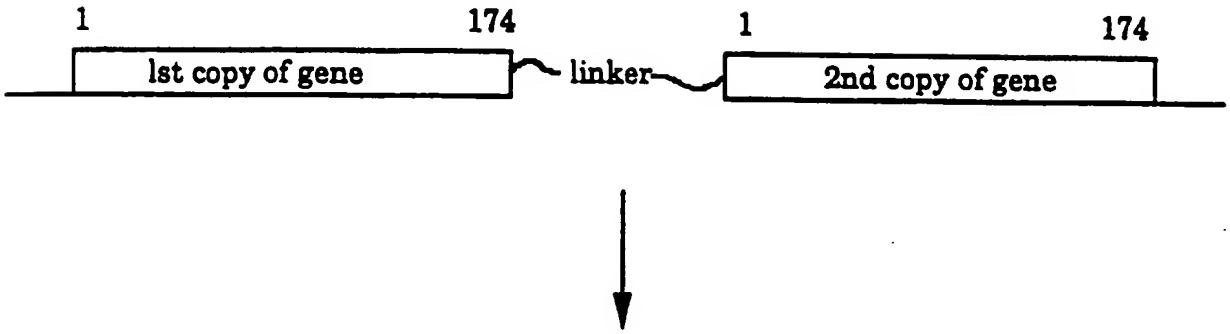

first step PCR amplification
new start
1
97
174
P-bl start
second step PCR amplifcation
P-bl stop
1
96
174
new stop
97
174
1
96
ligate fragments
97
174 ; 1
96

Figure 3.

I. Construct tandemly-duplicated template



II. PCR-amplify tandemly-duplicated template

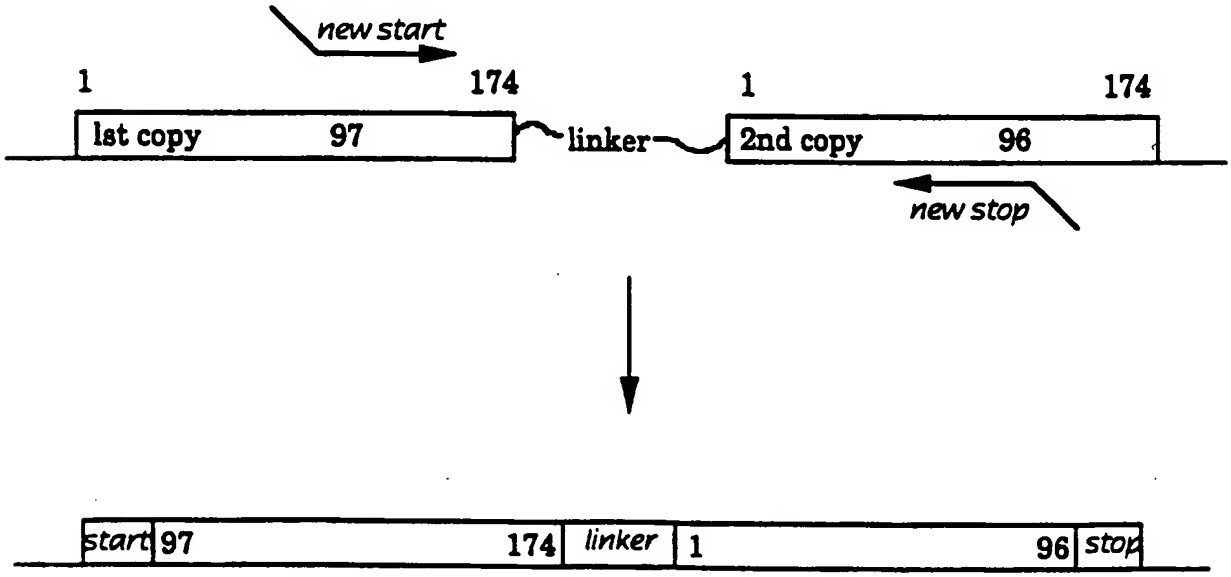


Figure 4.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC1/US 96/15935

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/19 C07K14/535 A61K38/19 C12N5/06 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 116, no. 13, 29 June 1994, DC US, pages 5529-5533, XP002024483 LEISHA S. MULLINS ET AL.: "Transposition of protein sequences: Circular permutation of Ribonuclease T1" cited in the application see the whole document ---	1
A	EP 0 396 158 A (KIRIN-AMGEN, INC.) 7 November 1990 see page 3, line 33 - page 4, line 35; example 8 ---	1-24
A	EP 0 299 782 A (SCHERING BIOTECH CORPORATION) 18 January 1989 see page 3, line 5 - page 9, line 55 ---	1-24
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1997	14.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Montero Lopez, B

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC:/US 96/15935

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 95 27732 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 19 October 1995 cited in the application see page 4, line 1 - line 31 see page 11, line 1 - page 17, line 7 see page 20, line 2 - line 16; figure 1; example 6 -----	1,2,4,5, 8-24

INTERNATI NAL SEARCH REPORT

International application No.
PCT/US 96/ 15935

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 12, 13, and 16-24 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 96/15935

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-396158	07-11-90	US-A-	4810643	07-03-89
		AU-A-	6334686	10-03-87
		AU-A-	6937391	02-05-91
		AU-A-	7575994	22-12-94
		CY-A-	1642	06-11-92
		EP-A-	0237545	23-09-87
		HK-A-	71892	25-09-92
		JP-A-	8231412	10-09-96
		JP-A-	2042998	13-02-90
		JP-B-	2527365	21-08-96
		JP-C-	1729335	29-01-93
		JP-A-	2031675	01-02-90
		JP-B-	4002599	20-01-92
		JP-A-	6090751	05-04-94
		JP-A-	6181791	05-07-94
		JP-B-	3031437	07-05-91
		JP-T-	63500636	10-03-88
		NO-A-	954199	22-04-87
		WO-A-	8701132	26-02-87
		US-A-	4999291	12-03-91
		US-A-	5582823	10-12-96
		US-A-	5580755	03-12-96
		BG-A-	60169	15-11-93
EP-A-299782	18-01-89	AU-A-	2131688	13-02-89
		CA-A-	1335717	30-05-95
		DE-A-	3880032	13-05-93
		EP-A-	0370052	30-05-90
		IE-B-	63514	03-05-95
		JP-B-	8002310	17-01-96
		JP-T-	2502877	13-09-90
		WO-A-	8900582	26-01-89
WO-A-9527732	19-10-95	AU-A-	2285795	30-10-95
		CA-A-	2187283	19-10-95
		EP-A-	0754192	22-01-97